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# ARCHIVES OF PATHOLOGY

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## THROMBO-ANGIITIS OBLITERANS

### EXPERIMENTAL REPRODUCTION OF LESIONS \*

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In 1914, in a paper<sup>1</sup> entitled "Is Thrombo-Angiitis Obliterans an Infectious Disease?" my views regarding the nature of the pathologic process in this strange malady were definitely stated, and there, as in previous communications, the avenues of research through which proof of this contention could be expected, were clearly indicated. It was my belief, first, that the acutely inflamed veins and nodosities of thrombo-angiitis obliterans could furnish the material in which an infectious agent-virus or micro-organism might reside and be brought to light; second, that these foci might be utilized for the reproduction of the disease or, at least, of some of the acute lesions of the malady.

With this in mind, I conducted researches over a period of years (ten or more) with little success, both because the material was scant and because the methods used were faulty.

Cases of thrombo-angiitis obliterans, in the stage of migrating phlebitis, were seen from time to time, but some of the patients refused to allow the excision of the acutely inflamed veins, and others presented themselves at a time when the acuity of the process had already subsided.

Having failed to discover a micro-organism, I turned my attention to the reproduction of the "acute lesions."

It may be succinctly stated here that it is possible to reproduce lesions identical with those of acute thrombo-angiitis obliterans, acutely inflamed veins with miliary giant cell foci, in the superficial veins of the upper extremities of man, by transplantation of the coagulated contents of acutely affected veins when in the phase of migrating phlebitis.

I shall not, in this paper, delve deeply into a critical discussion of the conclusions that may be drawn from such experimentation, but shall content myself with a brief statement of my results in (1) simple ligation of the veins of the forearm or arm for control purposes, (2) implantation or inoculation of acute thrombo-angiitis obliterans coagulum into the lumen of ligated veins, (3) implantation of acute thrombo-angiitis obliterans coagulum against the walls of ligated veins in man and (4) implantation (as in 3) in monkeys.

\* Submitted for publication, Oct. 3, 1928.

1. Buerger, L.: Surg. Gynec. Obst. **10**:582 (Nov.) 1914.

## SIMPLE LIGATION

Having elsewhere emphasized the importance of stasis in the production of all thrombotic vascular conditions, and mindful of the importance of limiting the spread of suspected infectious material to the confines of the vein used for the experiment, I decided to isolate a vein, under procaine hydrochloride anesthesia, and doubly ligate it, including between the ligatures from one-half to an inch or more of its length, without disturbing its continuity. Whenever necessary, lateral tributaries were also

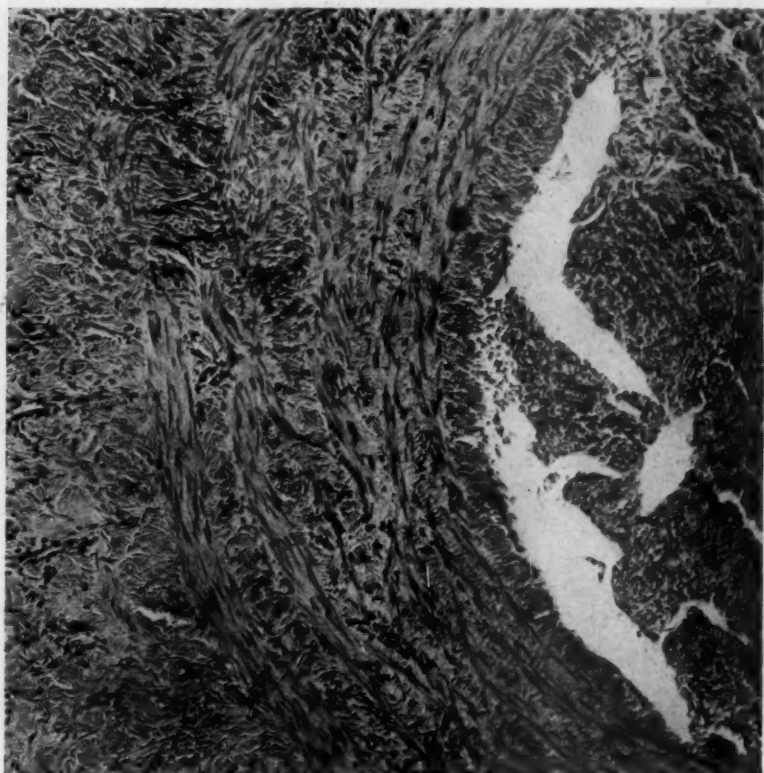


Fig. 1.—A part of the wall of a ligated vein of the forearm of a patient with thrombo-angiitis obliterans. On the right may be seen the bland organization of a clot; in the middle, the wall of the vein without any sign of acute inflammation, and on the left, connective tissue about the vein.

tied off, and the lumen of the excluded vein was allowed to become somewhat overdistended with blood. In order that the vein might escape the influence of immediate contact with the repair tissue that would develop in and under the incision, the incision was placed about 1 cm. to either side of the vein, and the isolation of this structure accomplished by a technic of undermining.

These experiments were conducted in (a) persons without vascular disease, (b) persons with thrombo-angiitis obliterans and (c) persons

with moderately pronounced arteriosclerosis, a vein of the forearm being employed in each case.

After from nine to twelve days, the veins were excised under local anesthesia, found thrombosed and examined microscopically.

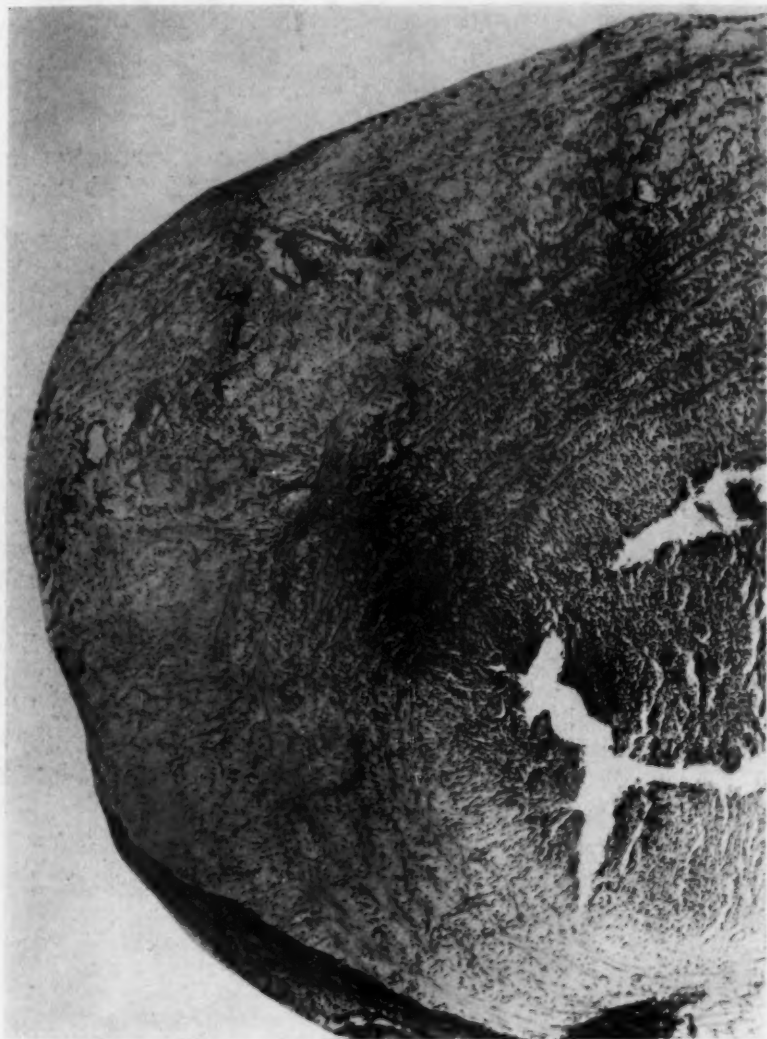


Fig. 2.—The acute inflammation of the wall and the inflammatory type of clot that are produced in a vein by paravascular implantations of clot from cases of thrombo-angiitis obliterans.

Bland thrombosis was regularly found in all instances. Whenever there was the slightest suspicion of infection of the wound, even if only

excessive reddening of it was encountered, the experiment was not included in the series.

Figure 1 illustrates a part of the wall of a ligated vein of a patient with thrombo-angiitis obliterans in the quiescent stages. On the right is a noninflammatory organizing thrombus adjoining a part of the vein wall. The latter does not show any sign of acute inflammation.

#### INOCULATION INTO THE LUMEN OF A VEIN

For about ten years I have had occasion from time to time to inoculate the veins of monkeys with emulsions of a coagulum taken from veins involved in the process of acute migrating phlebitis of the thrombo-



Fig. 3.—A higher magnification of the section depicted in figure 2.

angiitis obliterans variety but without success. More recently (since 1926), I have repeated these experiments using human veins, with the full consent of those whose veins were employed, precautions having been taken as follows: first, the vein was tied off centrally and distally; second, all tributaries were also ligated, and, third (to date), only persons who had had thrombo-angiitis obliterans many years before, but in whom symptoms were quiescent, were inoculated.

The technic was briefly this: As soon as a person with acutely migrating phlebitis of the thrombo-angiitis obliterans variety presented himself, presumably less than a week after the onset of the lesion, his consent was obtained for the removal of a portion of an acutely inflamed and thrombosed vein. As much material as possible was removed. The excised vein was opened longitudinally, its clot lifted out



and placed in a sterile watch-glass containing a few drops of saline solution. With a sharp knife, the inner wall of the vein was also scraped, and whatever adhered to the knife was mixed into the clot as the latter was being broken up in the watch-glass. With the tissue suspension made as fine as possible, this mixture was aspirated into a small syringe. The patient into whose vein this material was to

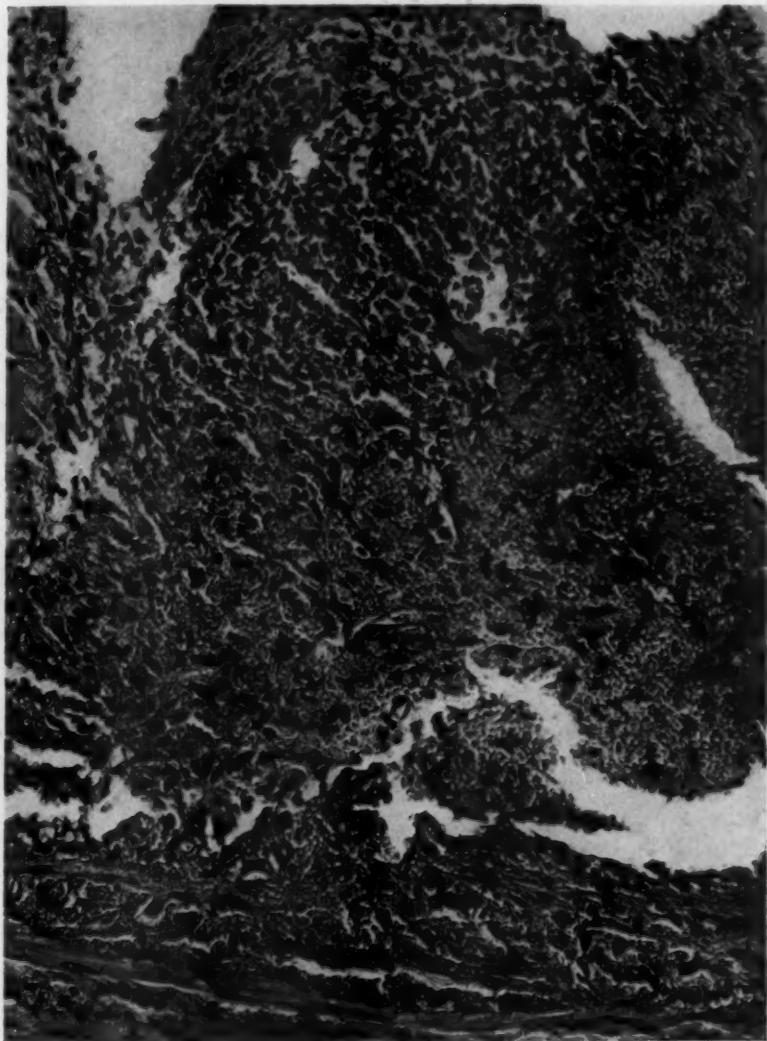


Fig. 4.—A miliary focus with giant cell is to be seen above and the wall of the vein at the bottom of the picture; this is taken from another case in which lesions typical of thrombo-angiitis obliterans were reproduced.

be inoculated had been made ready on another table. Inoculation into the ligated vein, after it was moderately filled with blood, was accomplished by an oblique insertion of the needle through the wall of the vein and into its lumen.

All these experiments were failures. When the veins were excised from seven to twelve days later, a sanious mixture was found to be the vascular content.

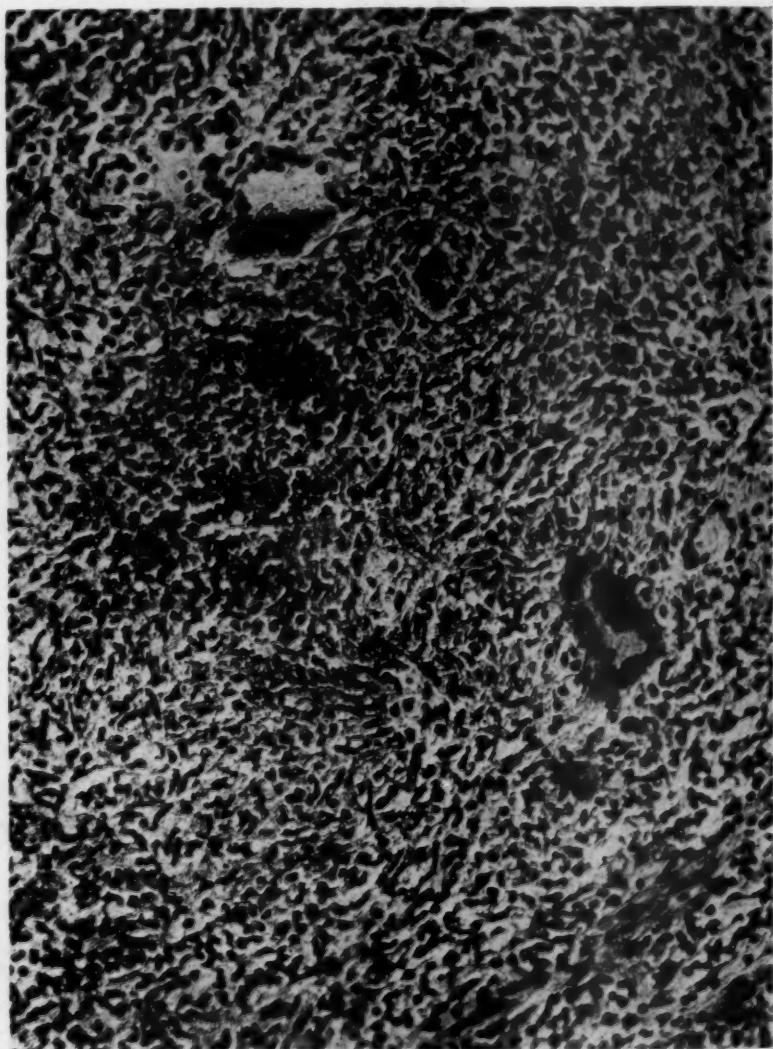


Fig. 5.—Another section from the case illustrated in figure 4, showing several giant cells.

#### IMPLANTATION OF THE COAGULUM ITSELF IN THE HUMAN VEIN

It became evident that the intravascular introduction of the suspected infectious material, because of its failure to permit of thrombosis, alone,



if for no other reason, must be substituted by a procedure that would not interfere with the clotting process. Therefore the following method was devised.



Fig. 6.—A low magnification of a section from the forearm and vein in another case in which lesions of acute thrombo-angiitis obliterans were reproduced.

Fresh material was sought and removed, as before, in aseptic fashion, but the clot was placed in a dry watch-glass or Petri dish, the scrapings from the intima remaining on the knife blade.

With the vein to be inoculated, isolated and ligated as in previous experiments, and the incision placed at least 1 cm. on either side and parallel to the course of the vein, the material was introduced partly underneath, partly on the side or over

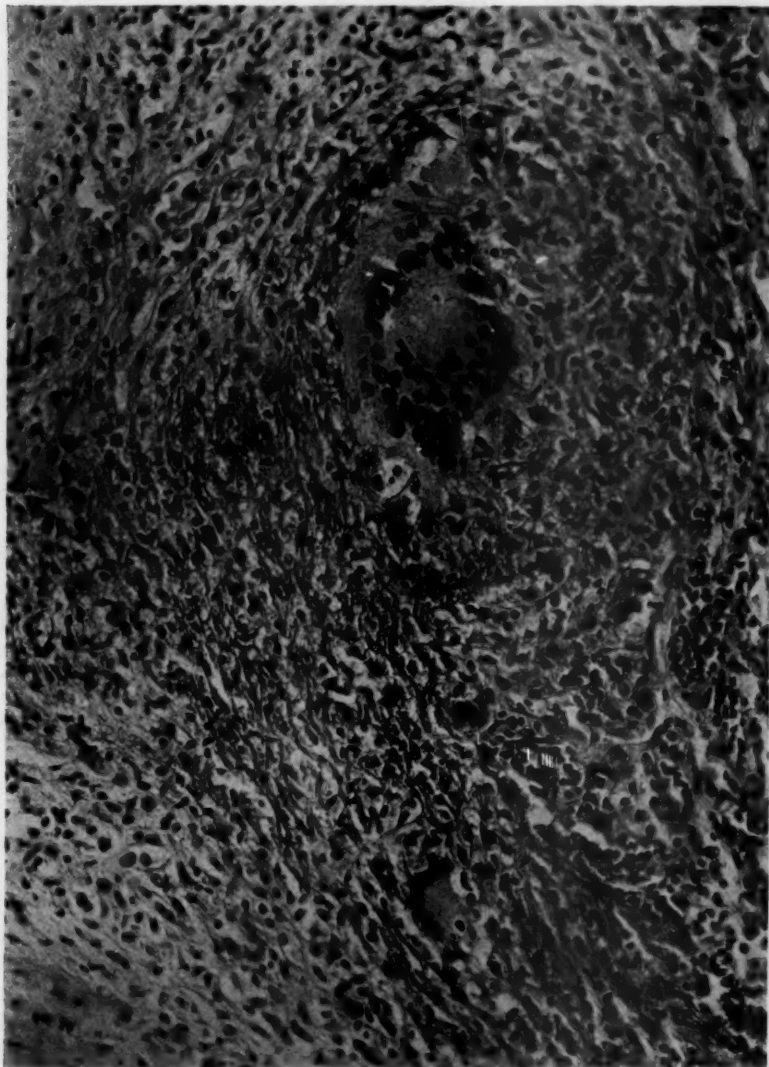


Fig. 7.—A high magnification of a portion of the same section shown in figure 6, presenting the same large giant cell referred to in the legend for figure 4. The wall of the vein is diffusely inflamed and the obturating clot contains a large giant cell.

the vein, and the smear of scrapings on the knife blade rubbed on the adventitia, which was sometimes lightly scraped or traumatized with the blade.

The skin was then sutured, great care being exercised that in this procedure such pressure was not exerted as might displace the fragments of the coagulum from their contact with the vein itself. Catgut other than that required for the

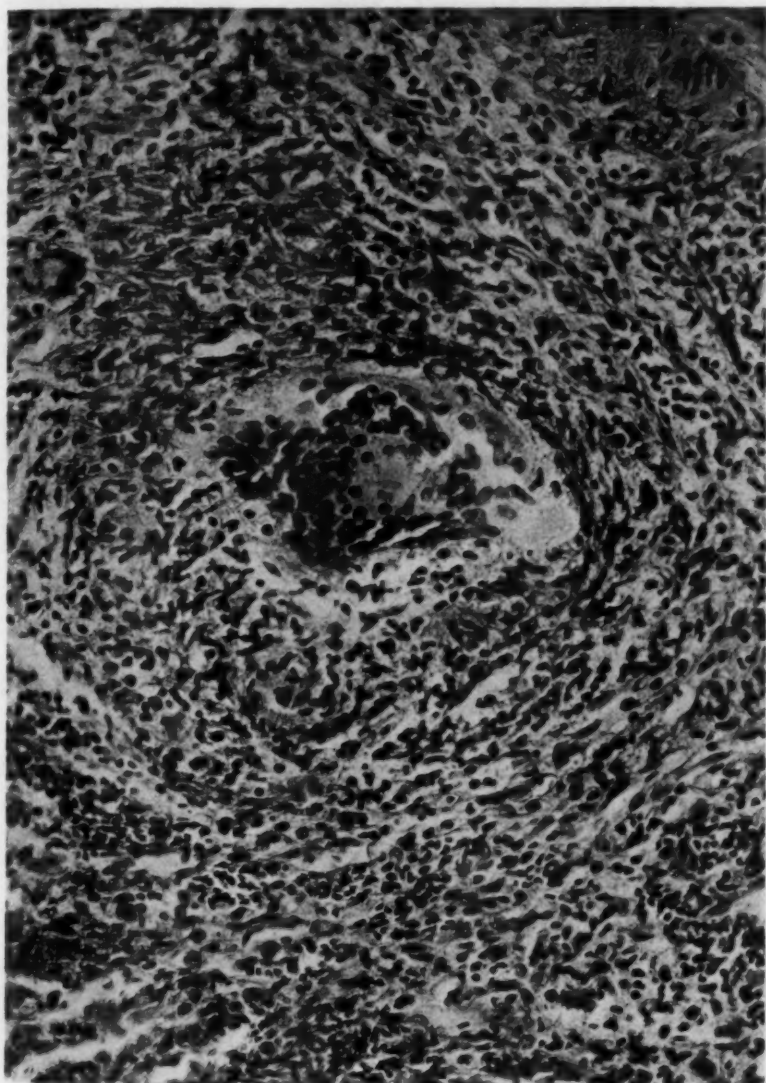


Fig. 8.—A high magnification of another portion of the section shown in figure 6, presenting the same large giant cell referred to in the legends for figures 4 and 6. The wall of the vein is diffusely inflamed and the obturating clot contains a large giant cell.

ligation of the vein was not employed, and filaments of gauze were not left in the wound lest they should act as foreign bodies around which confusing foreign-body giant cells might develop.

In all cases, ligations without the implantations were carried out, as controls.

The usual evidences of a mild nonpurulent phlebitis developed in at least four of eight cases. In two of the eight cases, a slight infection of the wound necessitated the rejection of the experiments; in two others, thrombosis occurred without any evidence of inflammation.

*Microscopic Examination.*—In a thrombosed vein excised from nine to twelve days after the implantation, lesions practically identical with those of acute thrombo-angiitis obliterans were found; namely, a diffuse polymorphonuclear infiltration of the wall of the vein and a clot containing typical miliary giant cell foci. The lesions in one case were particularly pronounced in a part of the wall of the vein, although polymorphonuclear invasion elsewhere was noteworthy (figs. 2 and 3). The clot showed rare giant cells but inflammatory foci especially marked in the vicinity of the most intense mural changes.

In another case, a typical miliary giant cell focus was seen shown in the upper part of figure 4, with the inflamed wall of the vein below and near the margin of the picture.

A section taken from the same vein at another level is depicted in figure 5, in which the giant cell foci of the clot are more strikingly represented.

In still another experiment, there was reproduced a picture almost the counterpart of that which has been regarded as characteristic of acute thrombo-angiitis obliterans (fig. 6). Higher magnification in figures 7 and 8 shows details that are conceded by most pathologists to be pathognomonic of the disease in question.

#### SIMILAR EXPERIMENTS IN MONKEYS

In two experiments in monkeys, I failed to produce other than bland thrombosis, a fact which would suggest that these animals may be immune. Other types of monkeys will be employed as soon as material becomes available.

#### CONCLUSION

The paravascular implantation of clot from cases of acute thrombo-angiitis obliterans was followed by the development of typical lesions in the apparently healthy ligated veins of the inoculated person.



ALLERGIC REACTIONS OF THE RABBIT'S INTESTINE DURING ANAPHYLACTIC SHOCK AS RECORDED CINEMATOGRAPHICALLY \*

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Since the fundamental paper by W. H. Schultz<sup>1</sup> on the reaction of the smooth muscle of the guinea-pig sensitized with horse serum and the subsequent studies by Auer and Lewis,<sup>2</sup> Dale,<sup>3</sup> Weil,<sup>4</sup> Coca,<sup>5</sup> Manwaring and Kusama,<sup>6</sup> Koessler, Lewis, and Walker<sup>7</sup> and others, it is now generally accepted as established that the isolated sensitized, non-striated muscle tissue will give strong contractions when brought into contact with the specific antigen. However, so far as we know, little, if any, work has been done on the response of the intestine of a sensitized animal in situ. The reaction of nonstriated muscle being so general and so vigorous, it was thought of interest to observe the change in physiologic response of the intact intestine of the rabbit.

METHOD

Ten rabbits were sensitized to horse serum. Each of the animals received four injections of 5 cc. of horse serum subcutaneously at intervals of from four to five days. Following the last injection, a period of from twelve to fourteen days was allowed to elapse before the toxic dose was given (intravenously). Two normal rabbits were used as controls.

For the observation of the intestinal reactions, the following method elaborated by us\* was used: The spinal cord was severed in the lower thoracic region under ether anesthesia. Following the animal's recovery from the effects of the ether, a laparotomy was performed on it in the now insensitive ventral abdominal wall. By means of a special trough with its supports, a leak-proof

\* Submitted for publication, Sept. 26, 1928.

\* From the Departments of Pathology and Pharmacology of the School of Medicine of Western Reserve University.

1. Schultz: *J. Pharmacol. & Exper Therap.* **1**:549, 1909.

2. Auer, J., and Lewis, P. A.: *Acute Anaphylactic Death in Guinea-Pigs*, *J. A. M.* **53**:458 (Aug. 7) 1909.

3. Dale: *J. Pharmacol. & Exper. Therap.* **4**:167, 1912.

4. Weil: *J. M. Research* **30**:299, 1914.

5. Coca: *J. Immunol.* **4**:219, 1919.

6. Manwaring and Kusama: *Abstr. Bact. Proc.* **1**:33, 1917.

7. Koessler, K. K.; Lewis, J. H., and Walker, J. A.: *Pharmacodynamic Actions of Bacterial Poisons*, *Arch. Int. Med.* **39**:188 (Feb.) 1927.

8. Ecker and Biskind: *Arch. Path.*, to be published.

pouch was formed of the abdominal cavity, which was then filled with liquid petrolatum at a temperature of 38.5 C. For lighting and for maintaining a constant temperature, we used a 15 ampere direct current carbon-arc lamp with a single condensing lens, which rendered the light beam approximately parallel. This beam was reflected from a mirror into the trough. Motion pictures were taken with a 16 mm. Bell and Howell camera.

To produce the shock, intravenous injections of varying doses of horse serum were given as recorded in the accompanying table.

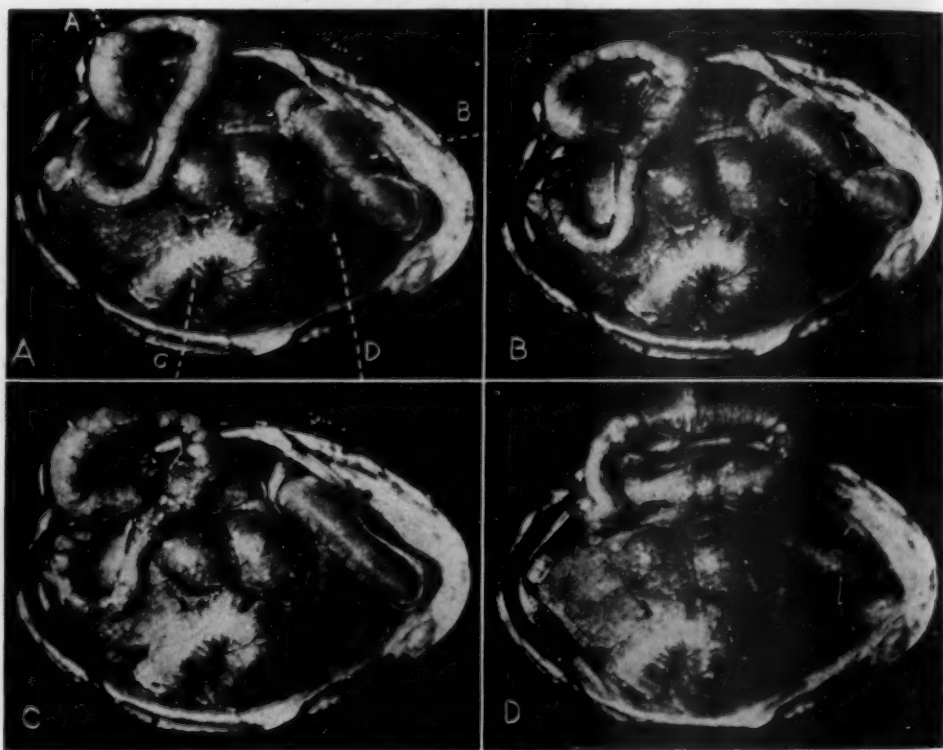


Fig. 1.—Enlargements from a 16 mm. motion picture film of the intestinal pouch of rabbit 2 showing (A) an incomplete peristaltic rush, and (B, C and D) irregular spastic constrictions in the small intestine and a high tone of the cecum. Note the propulsion in the lower colon. In A, a indicates the small intestine; b, the lower colon; c, the upper colon; d, the cecum.

#### EXPERIMENTAL RESULTS

All ten sensitized animals reacted to the injections of the doses of horse serum by increases in respiratory rates. Seven exhibited definite intestinal reactions. The two nonsensitized animals used as controls did not show any increases in respiratory rates or any intestinal excitation on the injections of the horse serum. There was no regularity in the doses required to produce the intestinal responses, in the intervals



following the injections before the reactions occurred, in the parts of the intestines that reacted or in the types and degrees of severity of the contractions. Two animals showed irregular spastic contractions and incomplete peristaltic rushes (*Rollbewegungen*) in the small intestine (fig. 1); one animal showed peristaltic rushes in the cecum (a rather rare phenomenon in the rabbit) and in the lower colon, together with local spasms in the small intestine (fig. 2); two animals showed peristalsis in the cecum only, and two animals exhibited a moderate reactivity of the small and large intestines. Three rabbits did not show definite intestinal excitation. From two to seven consecutive shock doses were given to each animal; the one receiving the seven doses (in

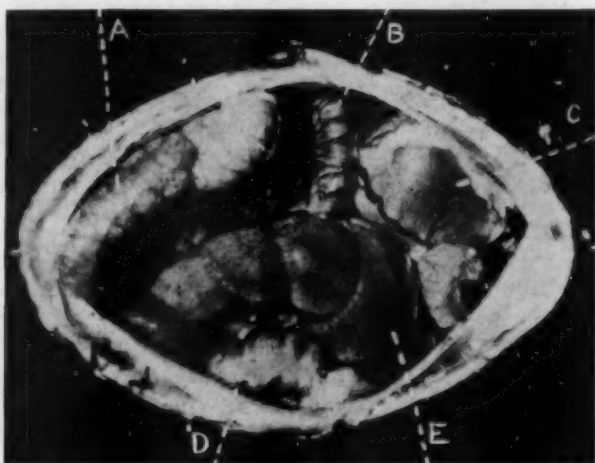


Fig. 2.—Enlargement from a motion picture film of the intestinal pouch of rabbit 7, taken during a peristaltic rush in the cecum. Note the prominent haustra in the upper colon and the high circular tone in the lower colon. Note also the distended bladder. A indicates the small intestine; B, the lower colon; C, the bladder; D, the upper colon, and E, the cecum.

a period of thirty-four minutes) reacted at each injection until the last. Other animals showed a similar response. In those animals in which the uterus was exposed, the horns were in a state of tonic contraction throughout the reaction.

That these results are of clinical significance in cases of allergy is evidenced by the following case, which came to our attention through the courtesy of Dr. Milton B. Cohen:

A white woman, aged 30, had had hay fever for ten years. For three successive years, she had had preseasonal courses of injections of an extract of grass pollen and had thus obtained marked relief from her symptoms. In the fourth year, following the subcutaneous injection of 0.2 cc. of a 1:1000 dilution of an extract of timothy pollen (1 gm. of timothy pollen in 20 cc. of a solu-

*Summary of the Allergic Effects on the Rabbit Intestine of Experimental Anaphylactic Shock*

Ex- peri- ment	Weight, Gm.	Time of the Severing of Spinal Cord	Time of the Lapar- otomy	Dose of Horse Serum, Cc.	Time of the Injec- tion	Reactions	Summary of Intestinal Reactions
1 ♂	2,300	10:50	11:30	5	11:56	Marked increase in respira- tory rate immediately	No definite excitation
				5	12:00	No further reaction; no definite intestinal excita- tion	
2 ♂	2,100	10:53	12:20	5	12:37½	At 12:38, spastic contrac- tions in some loops of small intestine and incom- plete peristaltic rushes in others; distinct increase in respiratory rate	Spastic constric- tions and incomplete peristaltic rushes in small in- testine
				5	12:50	During injection, same re- sponse as previously to 12:53	
				5	1:00	Same response	
3 ♂	2,000	9:25	10:00	5	10:30	At 10:30½, respiratory rate increased; slightly in- creased pendulum move- ments in small intestine	No definite excitation
				5	10:35	Cyanosis; strong contrac- tions of bladder; at 10:40, death	
4 ♀	2,150	9:27	10:45	5	11:02	Pendulum movements be- ginning in small intestine immediately; at 11:03½, rapid respiration; at 11:04, cyanosis; uterus white and spastic; defecation; at 11:05, circular contraction in colon; at 11:06, marked hour-glass constriction of bladder lasting 3 minutes	Moderate increase in tone and reactivity of both circular and longi- tudinal muscula- ture
				2	11:10	Further immediate increase in respiratory rate; at 11:11, considerable increase in circular tone of intes- tine; at 11:13, circular spasm in colon	
				2	11:14	At 11:17, ileum spastic	
				2	11:19	Respiratory rate again in- creased; defecation; at 11:21, more defecation	
				2	11:22	More defecation; increased pendulum movement in small intestine	
				5	11:27	More defecation; at 11:29, respiration rapid and labored; at 11:30, uterus still spastic; at 11:42 in- testine practically normal	
5 ♂	2,050	9:30	11:50	5	12:08	Respiratory rate moder- ately increased	No definite excitation
				5	12:12		
				5	12:14	Respiratory rate again in- creased, somewhat irregu- lar; slowed to normal in 1 minute	
				5	12:15		
6 ♀	2,200	9:19	10:15	5	10:27	Respiratory rate increased immediately; at 10:29, pendulum movement starts in small intestine; at 10:31, respiratory rate extremely rapid	Strong local spasms and incom- plete peris- taltic rushes in small in- testine
				2	10:35	Pendulum movement marked in 1 minute	
				3	10:40	Respiratory rate further increased	
				2	10:52	At 10:55, strong local spasms and incomplete peristaltic rushes in sev- eral loops of small in- testine	
				2	10:58	More spasms and rushes immediately	
				1	10:59	More spasms and rushes immediately	
				1	11:01	No further reaction	

*Summary of the Allergic Effects on the Rabbit Intestine of Experimental  
Anaphylactic Shock—Continued*

Ex- per- iment	Weight, Gm.	Time of the Severing of Spinal Cord	Time of the Lapar- otomy	Dose of Horse Serum, Cc.	Time of the Injec- tion	Reactions	Summary of Intestinal Reactions
7 ♂	2,450	9:20	11:15	5 5	11:26 11:26½	Increased respiratory rate; peristaltic rushes in cecum and lower colon, and local spasms in small intestine; at 11:30, another rush in lower colon	Peristaltic rushes in cecum and lower colon; local spasms in small intestine
				2 3	11:31 11:31½	Respiratory rate further increased; at 11:37, defecation	
				2 2	11:41 11:43	Reaction in colon More defecation	
8 ♀	2,040	9:24	11:50	10	12:03	Immediate and marked increase in respiratory rate; at 12:04, pendulum movement; at 12:05, peristalsis in cecum, pendulum movement in ileum	Peristalsis in cecum
				2	12:08	Respiration slow and shallow, heart rate slow; beginning contractions of bladder; at 12:10, peristalsis in cecum; at 12:13, death	
9 ♀	1,920	9:26	12:20	10	12:27	At 12:29, peristalsis in cecum, pendulum movements in small intestine, defecation; at 12:30, heart rate slow, no increase in respiratory rate	Peristalsis in cecum
				5	12:33	At 12:35, uterus extremely spastic and coiled up; considerable defecation; at 12:37, slight increase in respiratory rate	
10 ♀	1,800	9:30	12:45	8 5	12:51 1:05	At 12:55, rapid respiration Severe respiratory reaction lasting about 30 seconds; at 1:06, pendulum movement more marked, uterus coiled up	Mild reaction of circular musculature
				5	1:10	Severe respiratory reaction, lasting longer than previously; at 1:10½, middle colon spastic and longitudinally striated	
				2.5	1:14	At 1:16, constrictions of upper gut; at 1:22, defecation; at 1:26, uterus a thin cord; at 1:27, propulsion in lower colon	
11 Control ♀	2,000	2:45	3:30	10 5	3:37 3:47	No reaction Mild circular contractions in one loop of small intestine	No definite excitation
				5	3:52	Pendulum movement in one loop of small intestine	
12 ♂ Control	2,450	2:50	4:05	10	4:15	No definite excitation of intestine to 4:40	No definite excitation

tion containing glycerol, 66 per cent, and Coca's fluid, 34 per cent), a severe and unusual reaction occurred within ten minutes. The usual respiratory and skin signs were mild, but there was marked abdominal pain, with nausea, projectile vomiting and a desire to defecate. Examination of the abdomen revealed visible peristalsis. Two injections of epinephrine, each 0.4 cc. of 1:1,000, and one of morphine sulphate  $\frac{1}{4}$  grain (0.016 Gm.) and atrophine sulphate  $\frac{1}{150}$  grain (0.0019 Gm.), were required to control the reaction. This lasted ninety minutes, and was followed by the passage of mucoid stools.

## SUMMARY

Direct observation and cinematographs of the rabbit intestine during anaphylactic shock showed irregular spastic contractions and incomplete peristaltic rushes in the small intestine and peristaltic rushes in the cecum and the lower colon. In some animals, the reactions occurred on successive injections of the homologous protein. Two nonsensitized animals used as controls did not show excitation of the intestine following the injection of the protein. The uterine horns of the rabbits were also observed, and were found to be in a state of tonic contraction during the reaction. One clinical case of marked intestinal reaction during allergy is reported.

## RADIOACTIVE SUBSTANCES IN A BODY FIVE YEARS AFTER DEATH \*

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York University, Pathological Chemist, Bellevue and Allied Hospitals,  
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The literature dealing with the effects of radioactive substances in the human body is scanty. Martland,<sup>1</sup> in 1925, was the first to refer to it in American literature. He showed that a bombardment by certain radioactive substances resulted in necrosis of bone and a terminal aplastic anemia. Reports concerning the danger of the ingestion or injection of radium are likewise few in number. Plesch and Larczag<sup>2</sup> showed that thorium X brings about a cumulative action in the body. A fatal case of poisoning with thorium X was reported by Bickel<sup>3</sup> in 1912. In 1914, Gudzent and Halberstaedter<sup>4</sup> noted the danger of radioactive substances in certain industrial pursuits. Their article dealt with persons who handled radium, and constituted a treatise on its dangers, pointing out that an improper handling of it may result in local skin lesions and changes in the blood.

### REPORT OF A CASE

In the case here recorded, the body was exhumed five years after interment for the purpose of obtaining evidence in connection with the death of the girl and the illness of several others who had been

\* Submitted for publication, Nov. 9, 1928.

<sup>1</sup> From the Department of Pathology, Bellevue Hospital, and the Department of Chemistry, Washington Square College, New York University.

1. Martland, H. S.; Conlon, Philip, and Knef, J. P.: *Unrecognized Dangers in Use and Handling of Radioactive Substances: With Especial Reference to Storage of Insoluble Products of Radium and Mesothorium in Reticulo-Endothelial System*, J. A. M. A. **85**:1769 (Dec. 5) 1925.

2. Plesch and Larczag: *Handbuch der Radium Biologie und Therapie*, Berlin, Julius Springer, 1910.

3. Bickel: *Berl. klin. Wchnschr.* **49**:1322, 1912.

4. Gudzent, F., and Halberstaedter, L.: *Deutsche med. Wchnschr.* **40**:633, 1914.



employed at painting watch dials with luminous paint, the latter containing radioactive substances.

*History.*—A. M., an unmarried girl, was born in the United States on Dec. 21, 1897, of Italian parentage. The family history was negative, except that two sisters who worked in the same plant developed similar symptoms. The patient had been entirely well all her life except for minor illnesses. From November, 1917, to September, 1921, she was employed in a factory, painting watch dials with a mixture containing small amounts of radium and mesothorium; in the process of painting the watch dials, she "pointed" the brush between her teeth. In October, 1921, she had trouble with the teeth and complained of pains in various parts of the body; she became pale and lost some weight. At that time, she consulted a dentist who treated her teeth. The vague aches and pains, particularly pains in the joints, continued, and in March, 1922, she consulted a physician, who made a diagnosis of rheumatism and administered acetylsalicylic acid. A Wassermann test in January, 1922, was reported as negative. In June, 1922, another Wassermann test was reported to have been made with a 3 plus result. On the basis of this, a diagnosis of syphilis was made, and the patient was given seven intravenous injections of neoarsphenamine. By this time, she had developed necrosis of the lower jaw to such an extent as to require its almost complete removal. She became progressively worse and developed marked anemia. Records of blood counts taken at that time are not, however, available. Toward the close of her illness, she revealed a hemorrhagic tendency, bleeding frequently from the jaw, although purpuric spots were not noted. Death occurred on Sept. 12, 1922. The death certificate was signed "ulcerative stomatitis," and syphilis was given as a contributory cause.

*Autopsy.*—An autopsy was performed on Oct. 15, 1927. The surface of the body was fairly well carbonized; the body had been embalmed in the right brachial artery. The lower jaw was entirely missing, except for the coronoid process on the left side, which was taken as a specimen. This specimen was necrotic and brittle. Both upper jaw bones were removed in several pieces and taken as specimens. Necrotic foci were present along some of the alveolar processes. The left side of the face and the left side of the upper lip, which were well preserved, were also taken as specimens. The subcutaneous fat was decomposed, giving a distinct odor of butyric acid and having a soapy consistency. Lesions in the heart and the aorta could not be seen with the naked eye. The valves and the coronary vessels were smooth; a foramen was not present. The lungs were collapsed, but otherwise were well preserved; the bronchi were pale and somewhat granular. The liver weighed approximately 600 Gm.; on cross section, it was somewhat fatty and emitted a rancid odor. The gallbladder was collapsed, but did not show any gross changes. The spleen was small, soft and mushy, but otherwise did not show gross lesions. The kidneys were small and were embedded in a small amount of rancid fat; on cross section, they were found to be dark green; the markings were not distinct, and there was considerable postmortem change. The cortex of the suprarenal gland was well preserved; the medulla was soft and mushy, and was discolored greenish black. The bladder was collapsed. The uterus was small and virginal. The ovaries were small and did not show gross changes. The stomach was collapsed; it did not show gross changes. The intestines were collapsed; they contained a small amount of fecal residue. The esophagus was smooth and without gross changes. The thyroid was small and somewhat soft, but did not present other changes. The thymus was not present. The skull was sawed through the median line and both halves



of the brain were taken; the brain was firm and well preserved, and changes were not apparent to the naked eye. All the bones of the skull were removed for chemical analysis, as were also the second, third, fourth, fifth and seventh cervical vertebrae, portions of the fifth, sixth, seventh, eighth and ninth ribs on the right, both feet, the right femur, tibia and fibula and the left femur. The bones, after except the postmortem degeneration. Smears and sections of the bone-marrow did not show any recognizable cellular structures.

Microscopic examination of the viscera did not show any histologic lesions except the postmortem degeneration. Smears and sections of the bone-marrow did not show any recognizable cellular structures.

#### PHYSICOCHEMICAL WORK: THE ANALYSIS

*Preparation of the Bone Samples.*—Adhering tissue was removed as completely as possible from the bones by scraping them with a knife. The bones were then boiled for from two to three hours in a sodium

TABLE 1.—*Weights of Bones Before and After Drying, and After Reduction to Ashes in Preparation for Their Use in the Quantitative Estimation of Radioactive Substances*

Bones	Weight Before Drying, Gm.	Weight After Drying, Gm.	Moisture, Per Cent	Ash Obtained, Gm.	Ash, Per Cent
Upper jaw bone.....	4.34	3.995	8.0	1.890	41.8
Lower jaw bone.....	2.64	2.484	7.8	1.108	42.0
Vertebrae.....	4.46	3.705	10.9	2.390	53.5
Tibia.....	12.47	10.600	15.0	6.705	53.7
Femur (piece).....	25.90	21.750	10.0	13.700	53.1
Femur (piece).....	11.44	9.950	13.0	5.610	49.1
Skull (piece).....	8.91	7.350	17.5	4.770	53.5
Femur (piece).....	46.47	39.500	15.0	25.130	54.1

carbonate solution to loosen and soften adhering tissue; they were then thoroughly washed. Next, they were dried at a temperature ranging between 100 and 105 C. The long bones (tibia and femur) were sawed into lengths of from 1½ to 3 inches (from 2.5 to 7.6 cm.). The following bones were thus prepared: skull bone, upper jaw, piece of lower jaw, vertebrae, femur, tibia, metacarpals and phalanges.

*Preparation of Bone and Tissue Ashes.*—Bones as listed in table 1 were scraped and cleaned free of all muscle and fat tissue and wiped as dry as possible. They were weighed, then dried at from 95 to 100 C. to constant weight and finally ignited to a grayish-white ash and again weighed. The results are recorded in table 1. These ashes were used for the quantitative estimation of radium.

Weighed portions of tissue, as listed in table 2, were ground up, dried and ignited to a grayish-white ash. The ash so obtained was weighed. The values are recorded in table 2. The ash from the organs mentioned in table 2 was used in the electroscopic and photographic experiments.

*Presence of Radioactive Substance Determined with the Lind Electroscope.*—The normal leak was first determined by several trials. It was found to be as an average of 3,000 seconds for 10 divisions on the scale. The bone ash and the tissue ash were then successively introduced into the lower chamber of the electroscope and the leak determined. These leaks were always determined with the leaf between

TABLE 2.—*Weights of Organs Before and After Reduction to Ashes in Preparation for Their Use in Electrosopic and Photographic Experiments to Determine Presence of Radioactive Substances*

Organs	Total Weight of Organ, Gm.	Weight of Organ Ashed, Gm.	Ash Obtained, Gm.	Per Cent Ash	Calculated Ash from Whole Organ, Gm.
Liver.....	575	280	2.221	0.8	4.60
Lung.....	212	92	0.851	0.92	1.96
Spleen.....	55	26	0.246	0.95	0.52
Brain.....	485	122	0.590	0.49	2.35

TABLE 3.—*The Leaks Obtained for the Bone Ash and the Tissue Ash in an Experiment Determining Quantitatively the Presence of Radioactive Substances*

Material Tested	Gm.	Divisions	Seconds
Normal leak.....	Control	10	3,000
Femur (head).....	21.75	10	25
Femur (shaft).....	9.95	10	78
Skull bone.....	7.35	10	153
Vertebrae.....	3.70	10	45
Femur (shaft).....	11.52	10	61
Jaw (upper).....	9.58	10	47
Jaw (lower).....	5.02	10	66
Liver (ash).....	2.22	10	310
Spleen (ash).....	0.24	10	171
Brain (ash).....	0.59	10	104
Lung (ash).....	0.85	10	65
Femur (bone ash).....	1.00	10	192

TABLE 4.—*The Leaks Obtained for the Bones and Tissue Ashes of Normal Persons*

Material Tested	Gm.	Divisions	Seconds
Normal leak.....	Control	10	3,000
Jaw bone.....	12.50	10	2,980
Vertebra.....	5.15	10	2,890
Femur.....	22.95	10	2,910
Liver (ash).....	3.50	10	2,930
Brain (ash).....	0.95	10	3,010
Spleen (ash).....	0.50	10	2,920

6 and 8 of the scale, making successive readings strictly comparable. The results are indicated in table 3. The figures show an enormous reduction in the leakage time, indicating that all the bones and all the tissue ashes examined, without exception, were strongly radioactive.

Bones and tissue ash of normal persons were then tested with results as shown in table 4. The values are practically the same as the natural leak, showing the absence of radioactivity.

The earth taken from around the coffin was dried and also tested, with results as recorded in table 5. These results do not indicate any appreciable radioactivity.

*Presence of Radioactive Substances Determined by Photographic Method.*—All operations were performed in a dark room. A series of x-ray films were enwrapped in black photographic paper and sealed, to make them light proof. On these were placed various bones and tissue ash, also normal bones for controls. They were allowed to remain in this manner for ten days. If radioactive, the bones and the tissue ash would emit rays, and the beta and the gamma rays would penetrate the black paper and affect the photographic films. After ten days, the films were developed and printed. The results are shown in the accompanying photographs. Those on which normal bones were placed are not shown, because they did not show any impression.

TABLE 5.—*The Leaks Obtained for Earth from Around the Coffin*

Material Tested	Gm.	Divisions	Seconds
Normal leak.....	Control	10	3,000
Earth in box.....	50	10	2,000
Earth 1 foot below.....	50	10	2,540
Earth on top.....	50	10	2,650

A few films were wrapped in sheet lead (size 0.3 mm.) ; bones were placed on them and they were kept in a dark room. These did not show any effect after two weeks. They were then left standing for three months, at the end of which time a good picture was obtained. This impression was due solely to the gamma rays, as the alpha and the beta rays were completely screened off by the lead. This picture is also shown (part 4 of plate).

Every piece of bone, as well as every tissue ash that we examined, showed radioactivity by the photographic method.

*Presence of Alpha, Beta and Gamma Rays Determined.*—Radium emits three kinds of rays: alpha, beta and gamma rays. If a radioactive substance is placed in the chamber of the electroscope, the leak produced is due to the total effect of all three rays. If the radioactive substance is completely enclosed in sized paper, the alpha rays are withheld and the leak produced is due to the beta and the gamma rays only. If the radioactive substance is enclosed in a lead chamber, both the alpha and the beta rays are withheld and the leak produced is due to the gamma rays only. This experiment was tried with results as shown in table 6. It indicated that all three rays were coming from the bones.



1



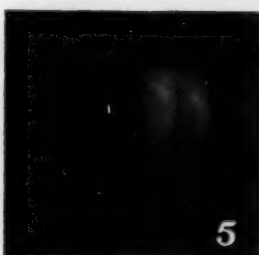
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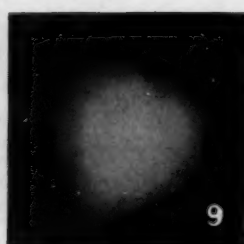
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10

Radium rays from various tissues of the body five years after death in a case of industrial contact with radium: 1, piece of lower jaw; 2, vertebra; 3, femur; 4, femur through lead; 5, tibia; 6, liver; 7, metacarpal bone; 8, brain; 9, lung, and 10, spleen ash.

*Determination of the Nature of the Active Deposit.*—A sample of femur (1 Gm.) was dissolved in strong hydrochloric acid. The emanation was plated off on a copper wire, suspended above the solution. The wire was charged negatively, 135 volts potential with respect to the solution. After thirty minutes, the wire was removed, placed in the charged electroscope and the leak determined. The change of the leakage rate was determined as a function of the time, thus giving a measure of the rate of decay of the deposit thus obtained. The values are indicated in table 7.

This experiment showed that the leakage time was shortest at the beginning, and then steadily increased, meaning that the deposit was

TABLE 6.—*The Leaks Obtained for Bone (1) Without Shutting Off the Radioactivity, (2) with Alpha Rays Withheld and (3) with Alpha and Beta Rays Withheld*

Material Tested	Divisions	Seconds
Natural leak .....	10	3,000
One vertebra, as such.....	10	22.5
Same vertebra enclosed in paper.....	10	68
Same vertebra enclosed in lead.....	10	606

TABLE 7.—*Results in Determination of the Nature of the Deposit of Radioactive Substance in the Bone*

Time at Which Readings Were Taken, A. M.	Time for One Division, Seconds
10:00.....	(Plating stopped)
10:01.....	130.2
10:05.....	195.0
10:12.....	245.2
10:21.....	274.6
10:31.....	328.4
10:44.....	337.1
11:21.....	431.8
Normal leak this day.....	442.0

most active at the beginning. Radium emanation produces just such an effect. With mesothorium, the leakage time at first decreases and then, after from three and one-half to four hours, it gradually increases. The picture obtained from the emanation in this bone indicated that it was an emanation from radium.

#### QUANTITATIVE WORK

*Quantitative Calibration of Electroscope in Terms of Ore of Known Radium Content by Emanation Method.*—The Lind electroscope was used for all the measurements in this investigation. It was calibrated by the emanation method, as follows:

A sample of carnotite ore weighing 1 Gm. and containing 1.58 per cent uranium was placed in a 200 cc. round bottom flask, covered with 100 cc. of 1:1 nitric acid



and saturated with barium nitrate and the flask content was boiled to expel all the emanation. With the content of the flask at boiling temperature, the flask was sealed and the emanation allowed to collect for a period of one week. After this time, the sealed flask was connected with a purifying train (to remove carbon dioxide, acid spray and moisture) and the emanation was driven over into a previously evacuated ionization chamber. The emanation was allowed to stand in the chamber for three hours before measurements were begun, in order to allow it to come to equilibrium with its surroundings. The electroscope head was then mounted on the ionization chamber and charged for fifteen minutes at 135 volts, and the rate of leak determined. The average of several determinations gave 14.4 seconds for 10 divisions leak. Since the natural leak of the instrument is 3,000 seconds per ten divisions, the latter is not of significance as a corrective factor.

Since the ore contained 1.58 per cent uranium, the amount of uranium present was  $1 \times 0.0158 = 0.0158$  Gm. uranium.

The radium to uranium ratio—that is, the amount of radium element in equilibrium with 1 Gm. of uranium—is accurately known and has the value

$$\text{Ra/U} = 3.33 \times 10^{-7}$$

It is known, however, that only 97 per cent of this amount gives off emanation, so that the corrected amount of radium equivalent to the aforementioned sample and measured as stated is:

$$\begin{aligned} \text{Radium} &= 0.0158 \times 3.33 \times 0.97 \times 10^{-7} \\ \text{Radium} &= 5.06 \times 10^{-9} \text{ Gm.} \end{aligned}$$

This amount of radium, then, gives the observed leak of ten divisions in 14.4 seconds.

*Quantitative Determination of Radium on Several Tissue and Bone Ashes by the Emanation Method.*—One gram samples of ash were treated exactly the same as was the carnotite ore in the calibration. The rate of leak was determined in each case. From the calibration just described, it was found that  $5.06 \times 10^{-9}$  Gm. of radium causes ten divisions leak in 14.4 seconds. Hence, the radium content of this series was calculated by the following equation:

$$\frac{14.4}{\text{Leak time for 10 div. in sec.}} \times \frac{1}{\text{Wt. taken in Gm.}} \times 5.06 \times 10^{-9} = \text{Gm. Ra per Gm. of ash}$$

Table 8 shows the radium content of the bone ashes and the tissue ashes as determined by this method.

Assuming a body weight of 100 pounds (45 Kg.), 18.3 per cent of which was bone, the bone ash being 51 per cent of the bone proper, we found that the entire bone ash content in the body was 4,198.5 Gm. The total radium content in bones, liver, lungs, spleen and brain was, therefore, 48.4179 micrograms (table 9). It must be remembered, however, that this value for the radium content was from about 22 per cent of the entire body weight only.



## SUMMARY

A case is described in which radioactive substances were recovered from a human body five years after death.

The bones (jaw, vertebrae, femur, tibia, skull, metacarpal and phalanges), and the liver, brain, lungs and spleen were tested for signs of radioactivity. Every portion of tissue and of bone tested gave photographic evidence of radioactivity. Every portion of tissue and of bone tested gave electroscopic evidence of radioactivity. All three rays (alpha, beta and gamma) were detected.

TABLE 8.—*The Total Amount of Radioactivity in the Bone and Organ Tissues as Determined by the Emanation Method*

Bones and Tissues	Grams Radium per Gram of Bone Ash	Micrograms Radium per Gram of Bone Ash
Vertebrae.....	$2.12 \times 10^{-8}$	0.0212
Femur.....	$1.01 \times 10^{-8}$	0.0101
Upper jaw.....	$1.19 \times 10^{-8}$	0.0119
Skull.....	$0.37 \times 10^{-8}$	0.0037
Tibia.....	$0.63 \times 10^{-8}$	0.0063
Lower jaw.....	$1.58 \times 10^{-8}$	0.0158
Lungs.....	$2.76 \times 10^{-8}$	0.0276
Brain.....	$1.01 \times 10^{-8}$	0.0101
Spleen*.....	$1.03 \times 10^{-8}$	0.0103
Liver.....	$0.69 \times 10^{-8}$	0.0069

\* 250 mg. of spleen ash used.

TABLE 9.—*Estimation of the Total Radium Content of Bones and Organs Taken from Exhumed Body*

Tissues Used for Estimation	Weight of Ash from Entire Body, Gm.	Average Radium Content per Gm. in Micrograms	Total Radium Content in Micrograms
Bone.....	4,198.5	0.0115	48.282
Liver.....	4.6	0.0069	0.032
Lungs.....	1.95	0.0276	0.0538
Spleen.....	0.52	0.0103	0.0214
Brain.....	2.35	0.0101	0.0237
Total.....			48.4179

The nature of the emanation was found to be that of radium. Quantitative determination (by the emanation method) showed the presence of 48.282 micrograms of radium in the entire skeleton. The radium content was also estimated for the lungs, liver, spleen and brain. The total estimated radium content for entire bones, liver and lungs was 48.4179 micrograms.

## CONCLUSIONS

Radium salts that are absorbed find permanent lodgment in both the viscera and the bones, particularly the latter. The manner and course of its distribution cannot be stated with certainty, although there appears to be a predilection for lodgment in the bones. The bombardment of the bones by the radium rays causes increased brittleness and necrosis.

## OSTEOGENIC SARCOMA IN DIAL PAINTERS USING LUMINOUS PAINT \*

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Of some fifteen girls whose deaths were attributed to radium-mesothorium poisoning incurred while they were employed at painting watch dials with luminous paint, two were found to have osteogenic sarcoma of the bone.

The etiology, the general and the special symptomatology, the pathologic anatomy, the prognosis and the treatment in this new industrial hazard were first described by Martland and his associates in 1925 and 1926.<sup>1</sup>

Only a brief résumé of the observations on this disease is necessary in this paper.

The paint used consisted of crystalline phosphorescent zinc sulphide, ZnS (Sidot's blend), rendered luminous by the addition of extremely small amounts of radium, mesothorium and radiothorium. These radioactive substances were in the form of insoluble sulphates in the paint when it was used.

The mode of poisoning in these cases was by ingestion. Owing to a general habit among these workers of pointing their brushes in their mouths while painting the dials, they swallowed small amounts of the radioactive paint day after day. They were also exposed to radioactivity by absorption of the substance through the skin and by inhalation, especially of the dust of the luminous paint, but these portals of entry were not considered significant. The girls affected had swallowed the paint for periods of from one to four years or more.

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\* From the Pathologic Department of the City Hospital, Newark, N. J., and the office of the Chief Medical Examiner of Essex County, N. J.

\* Read before the New York Pathological Society at the New York Academy of Medicine, New York, March 8, 1928.

1. Martland, H. S.; Conlon, Philip, and Knief, J. P.: Some Unrecognized Dangers in the Use and Handling of Radioactive Substances (with Special Reference to the Storage of Insoluble Products of Radium, Mesothorium, etc., in the Reticulo-Endothelial System), *J. A. M. A.* **85**:1769 (Dec. 5) 1925. Martland, H. S.: Microscopic Changes of Certain Anemias Due to Radioactivity, *Arch. Path.* **2**:465 (Oct.) 1926. Reitter, G. S., and Martland, H. S.: Leukopenic Anemia of the Regenerative Type Due to Exposure to Radium and Mesothorium, *Am. J. Roentgenol.* **16**:161 (Aug.) 1926.

Most of the paint swallowed passed rapidly through the gastrointestinal tract and was eliminated. A small amount, however, was continually absorbed and eventually stored as insoluble sulphates of particulate or colloidal size in the main organs of the reticulo-endothelial system and, above all, in the bones. The exact mode of intestinal absorption is not clear. Whether the insoluble radioactive substance was picked up by wandering histiocytes of the intestine and taken into the thoracic duct, then to the blood and then to the storage organs, in which it was phagocytosed by the fixed histiocytes of the blood sinusoids, the Kupffer stellate cells of the liver and the splenic phagocytes; whether small quantities passed through the intestinal tract in a manner not understood, or whether the radioactive substances had some fixed position in the zinc sulphide molecule which allowed it to be absorbed with the zinc is unsettled at present. Perhaps the conceptions of absorption from the intestinal tract must be augmented and modified considerably. It should be recalled that the entrance into the body of insoluble matter of particulate size is thought to be easier by inhalation than by ingestion. For instance, in anthracosis, the foreign matter is readily picked up from the alveoli of the lungs by the phagocytic cells or histiocytes of the reticulo-endothelial system, and then by lymphatic drainage it is distributed over the entire lung and taken to the hilum nodes in enormous quantities. Anthracosis of the intestinal tract and its lymphatics is, on the other hand, unusual. The same anatomic pathways are seen in exogenous infection of the lung with human tubercle bacilli.

The deposits in the bones were generalized over the entire skeleton. One bone did not contain more radioactivity than another. A study of its minute distribution in the individual bones (which, on account of the extremely small amounts present, could be determined only by photographic methods) showed an irregular distribution in the bone and often a concentration in certain portions. The outer layers of the cortex seemed to be the final position of storage. Here it was frequently stored in large amounts and probably replaced calcium in these areas.

After final deposition in the bones, these deposits emitted their characteristic radiations day after day (every minute of the twenty-four hours), month after month, and year after year. As about 95 per cent of the radiation coming from these deposits was alpha and only 5 per cent beta and gamma, the blood-forming centers, owing to their proximity, were constantly bombarded by the alpha particle, exposing vital centers to a type of radiation never before known to have occurred in human beings.

The alpha particles are probably the most potent and destructive agent known to science. They consist of nuclei of helium atoms containing two positive charges ( $\text{He}^{++}$ ) ejected from the radioactive

substances with great force, attaining an initial velocity equal to from one twentieth to one twelfth that of light. Aside from the beta rays, which are negative electrons and much smaller, they represent the fastest space-occupying objects yet known. They collide with other atoms with terrific impact, usually jerking off a negative electron. The chemical changes resulting from this ionization are of the ordinary molecular character. Occasionally, the alpha particle may strike the atomic nucleus of lighter atoms, causing disruption with the liberation of a high velocity atom of hydrogen (H rays). Biologically, the alpha rays are much more destructive than either the beta or the gamma rays, the relation being 10,000 to 100 to 1, respectively. Therefore, radioactive elements in such small amounts that the beta and the gamma radiations are almost negligible still produce, through their alpha radiations, intense physiologic effects, if given by mouth or vein.

In addition, the preponderance of mesothorium in this paint is of great toxicologic importance for the reason that mesothorium in equilibrium with its radiothorium emits five alpha particles, whereas radium emits only four; also, the alpha particles of mesothorium and the products of its decay have a greater velocity and penetration than those of radium, and, therefore, are, chemophysically and physiologically, more active.

As a result of the continuous and constant radiation from the deposits on the blood-forming centers, especially of the deadly alpha rays, these centers in time became exhausted, and a leukopenic anemia, in most cases of the regenerative type, but occasionally of the aplastic or aregenerative type, developed. This anemia often proved fatal. Anemias previously recorded, due to external radiation, were all described as aplastic. This judgment was based almost entirely on clinical observations, unsupported by autopsy and histologic evidence, these being, unfortunately, lacking in almost every case. The alpha particle never entered into the etiology to any extent, as the radiation was almost entirely penetrative and chiefly due to gamma rays.

Due to a continuous radiation from the deposits, a radiation osteitis often developed in these cases, similar to that seen in bones as a result of large doses of external irradiation. Because of the proximity of the mouth—the dirtiest part of the body—to the mandible and the maxillae, a superadded bacterial infection, usually by way of the teeth, resulted in extensive, intractable necrosis of the jaw, which, together with the anemia, formed the outstanding clinical features of the early fatal cases.

In the later cases (at the time of writing the patients are still alive), a sufficient period of time had elapsed after the exposure (from six to seven years) to allow the mesothorium, which formed some 70 per cent of the radioactivity, to diminish in quantity by its own natural,



uninfluenceable decay to below one-half its strength (6.7 years, half period). In the later cases, therefore, the patients seemed to be escaping the extensive necrosis of the jaw and the fatal leukopenic anemias of the regenerative type. They showed, however, chronic crippling lesions of the bones the result of radiation osteitis, most marked in the bones that were subject to weight, pressure and trauma, such as the head of the femur and the acetabula, the spine, the scaphoid bone of the foot, etc. The anemias were milder, and, if progressive, were more apt to be of the aplastic or aregenerative type, and to be characterized at autopsy by a bone marrow similar to that seen in chronic benzol poisoning.

As regards the occurrence of sarcoma of the bone in these cases, unfortunately, in the first case, the clinical data are meager, and pathologic material is not now available. In this case, the girl died in 1924. A clinical diagnosis of osteogenic sarcoma of the femur was made from the symptoms and the roentgenograms. She was treated by deep roentgen therapy. The presence of sarcoma, however, was never proved by operation or autopsy.

In the second case, a diagnosis of osteogenic sarcoma of the scapula was made during life and proved at autopsy. After a fall, in which the patient hurt her right shoulder, a sarcoma of the scapula developed to which, in addition to a severe anemia, she succumbed. She never had severe necrosis of the jaw, but during life showed evidence of a radiation osteitis in the scaphoid bone of the right foot, in the heads of both humeri and in the glenoid cavities. Her bones after death were radioactive, and it appears plausible that the sarcoma originated in a bone that previously had been the seat of a radiation osteitis.

The incidence of two sarcomas of bone in fifteen cases of radium-mesothorium poisoning is too large to be passed over as due to coincidence. Since this is the first time to our knowledge that sarcoma of the bone has been attributed to radiation, the case is of sufficient interest to be reported.

#### REPORT OF CASE

*History.*—A woman, aged 33, worked as a painter of dials eight years before her death. When applying luminous material to watch dials, she was in the habit of pointing the brushes with her lips. She had little trouble with her teeth and never had any extensive necrosis of the jaw. Roentgenograms taken by a dentist in 1926 showed lesions, which we have interpreted as typical radiation osteitis, involving chiefly the alveolar portions of the mandible.

In September, 1926, fourteen months before her death, she fell while working in a department store, injuring her right shoulder. There was pain with limited motion, and she was later referred to the compensation department. Roentgenograms showed a slight downward displacement of the head of the humerus. She was operated on, but disease was not found in her shoulder. The wound healed promptly without complications.



In July, 1927, six months before her death, she still complained of pain in her right shoulder. She also had pain and localized tenderness over the scaphoid bone of her right foot. At this time, she was seen by one of us (H.). An examination of the original roentgenograms demonstrated peculiar changes in the right humerus, the scapula and the scaphoid bone of the right foot. He concluded that the condition resembled a radiation osteitis similar to that seen in other painters of dials. It was then ascertained that she formerly had been a dial painter.

In September, 1927, three months before her death, roentgenograms for the first time showed a sarcoma of the right scapula, springing from its anterior and upper portion, and an osteitis of the scaphoid bone of the right foot with fragmentation.

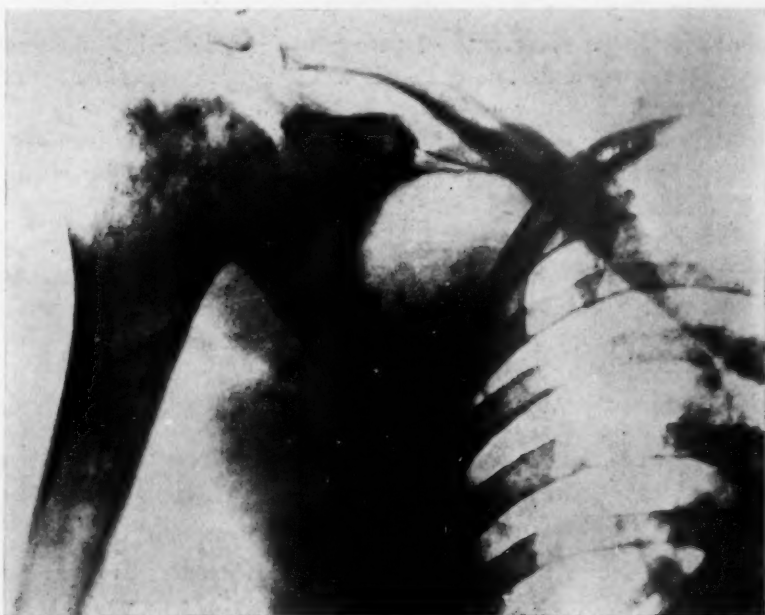


Fig. 1.—Roentgenogram of the right shoulder, taken five months before death. Evidence of a radiation osteitis may be noted in the head of the humerus, the acromium and the glenoid process.

In December, 1927, she returned to the hospital with her right upper extremity markedly swollen down to the hand. She had pain, which was constant and unrelieved by morphine. To lessen the pain, an operation was performed to relieve pressure on the main nerve trunks. Large masses of tumor tissue were removed. She died a few hours later. During life, tests were not made to prove the presence of radioactivity in her body, such as the examination of the expiratory air for the presence of emanation or an examination for the alpha particle by scintillation methods, or the use of the gamma electrometer for the demonstration of penetrative radiations coming from the body. The latter method, however, is of little use in these cases, on account of the extremely small amounts deposited in the bones.



Fig. 2.—Roentgenogram of the right shoulder, taken two months before death. An extensive, rapidly growing osteogenic chondrosarcoma may be noted springing from the anterior surface of the scapula and the glenoid process.

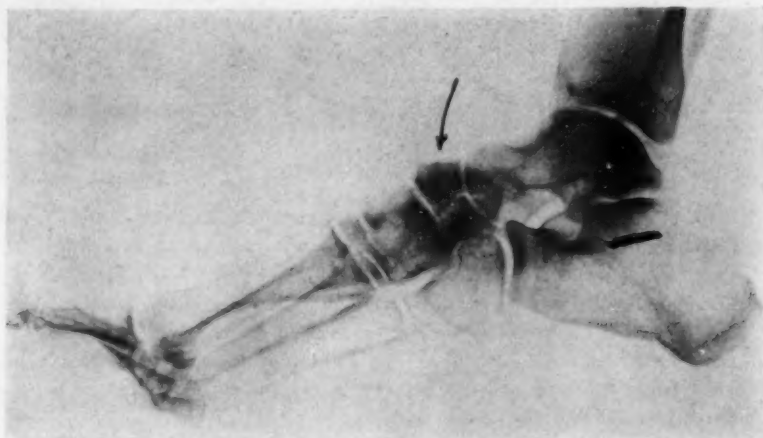


Fig. 3.—Roentgenogram of the right foot, taken five months before death. The dense periphery and fragmentation of the scaphoid bone may be noted. The patient had exquisite tenderness over this bone.

*Autopsy.*—A large osteogenic sarcoma of the right scapula was found, invading the whole anterior and upper part of the bone, with infiltration into the supraspinous and infraspinous muscles. Visceral metastases were not found. A profound anemia was present. The yellow marrow of the femurs was entirely replaced by dark red, apparently regenerating marrow.

*Histologic Examination.*—An osteogenic sarcoma was seen, in which there was considerable cartilage. In places, the growth was cellular, with mitotic figures and hyperchromatism; in other places, it was sclerotic. New formation of bone was common.

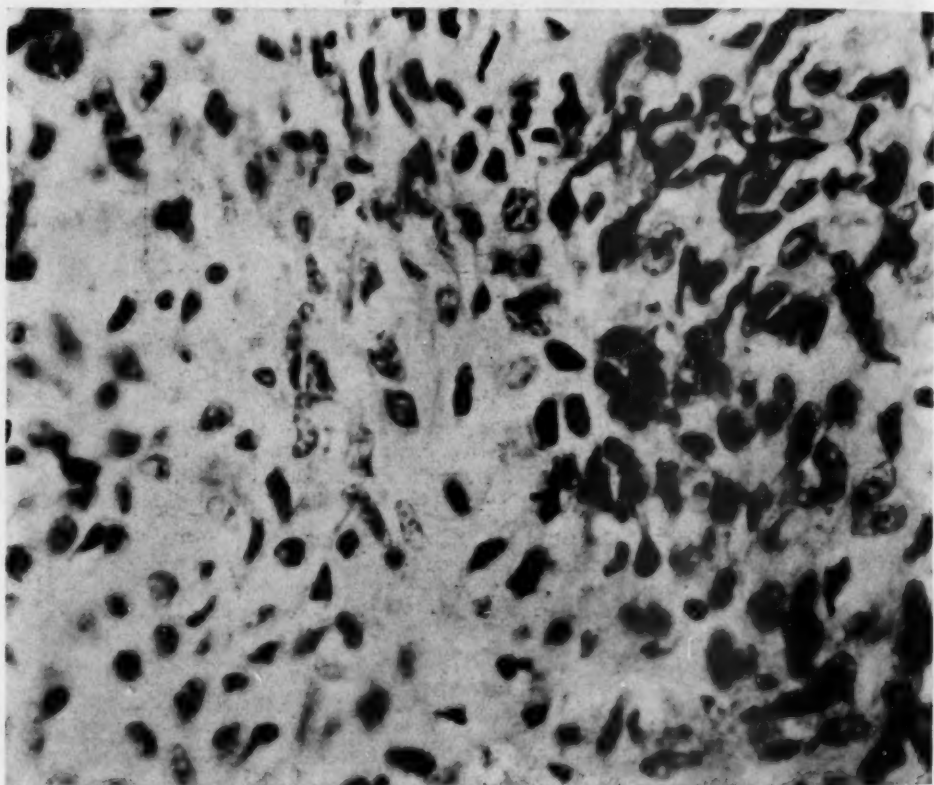


Fig. 4.—High power magnification of the osteogenic sarcoma tissue. Tumor mitoses and hyperchromatism may be noted.

The bone marrow showed a regenerative leukopenic anemia of the megaloblastic type, similar to that described as having occurred in three other fatal cases.<sup>1</sup>

Sections from the scaphoid bone of the right foot showed a radiation osteitis, the marrow being replaced by loose, gelatinous, myxomatous, fibroblastic tissue, in which there was considerable fat.

*Demonstration of Radioactivity in the Bones by Photographic Methods.*—Dental films in their original packets, when strapped to the bones, showed photographic impressions in from fourteen to thirty days. The outlines of metal clips, coins and the like placed between the bone and the surface of the film were clearly

visible. These shadowgrams were produced by beta and gamma rays coming from deposits in the bones, the alpha rays being screened and filtered out by the paper of the dental pack.

The bones, when placed directly on photographic plates or films, produced photographic impressions in as short a period as three days. After seven days' exposure, the irregular distribution of the radioactive deposits could be plainly ascertained with typical alpha penciling.

Bones incinerated to a white ash and given thirty days in which to regain their equilibrium, when placed on photographic films, produced photographic impressions in from two to three days' exposure. The sarcoma when ashed and treated similarly showed only faint radioactivity. This was undoubtedly due to the impossibility of separating portions of the scapula from the new bone formed in the osteogenic sarcoma.



Fig. 5.—Photographic impressions of the head of the humerus and the shaft made by laying dried bones directly on the film. The duration of the exposure was five days. The exposure is due to alpha, beta and gamma rays, since there was not any screening. The irregular concentration in the bones may be noted, especially the large amounts in the cortex of the shaft; also the typical alpha penciling. In this figure, there is a reversal of the black and white of the original negatives.

*Demonstration of Radioactivity in the Bones by Scintillation Methods.*—When portions of dried bone from various parts of the skeleton were held near a screen of phosphorescent zinc sulphide uncontaminated by radioactive substances and the screen was examined under a large magnifying glass, the latter showed typical scintillations. This was absolute proof of radioactivity; for each scintillation represented the light produced by the collision of an alpha particle (a double-charged nucleus of helium) against aggregates of zinc sulphide molecules. The bombardment of the alpha particle could undoubtedly have been heard if proper radio amplifiers had been used.

*Demonstration of Radioactivity in the Bones by Means of an Alpha Electro-scope.*—Samples of bones, after being dried in an electric oven, showed positive



evidence of radioactivity when placed in the lower chamber of an alpha electro-scope of the Lind type.

After the bones had been incinerated to white ash and had been given thirty days in which to regain their equilibrium, the increased leak due to radioactivity was easily demonstrable with the alpha electro-scope.

*Chemical Extraction with Determination of the Amount of Radioactivity.*—

After samples of bone had been incinerated in the electric oven to a white ash with an excess of carbon, a paste of the ash was made with barium chloride and hydrochloric acid. This was boiled with hydrochloric acid and distilled water and filtered while hot. The precipitate was dried, incinerated and after thirty days measured for radiothorium. Sulphuric acid was added to the filtrate, and, after being left to stand for precipitate, the mixture was boiled and then filtered while hot so that the calcium sulphate might be held in solution. The precipitate was again dried, incinerated and after thirty days measured for radium and mesothorium. By this method, a calculation was made, after a reading with the gamma electrometer against known standards, which showed that the entire skeleton in this case contained about 50 micrograms of radioactive substances, in which mesothorium predominated.

Concerning the amount of radioactive substance recoverable at autopsy in these cases, it is of interest to consider my previous experience. The amounts recovered were small. In the first case seen by one of us (M), that of a chemist who died from a rapidly progressing anemia of the regenerative type, the amount of radioactive substances present in the entire skeleton was estimated by the company's physicist to be about 14 micrograms, of which 45 per cent was radium and the remainder mesothorium. At that time we were not aware of the importance of the cases, and because of the restrictions placed on the performance of the autopsy, we were able to submit only a few of the lumbar vertebrae to the physicist for examination. In the next case, we had a better opportunity. By chemical methods, the radioactive substances were extracted, and it was estimated that the skeleton contained about 180 micrograms, of which 70 per cent was mesothorium and the products of its decay. In the third case, 150 micrograms of radioactive substances was found. In a case described by Flinn,<sup>2</sup> in which the gamma electro-scope was used during life, he estimated that about 100 micrograms was present in the body. In another case examined by St. George and Gettler, 48.282 micrograms was recovered from the bones, liver and lungs. It may be seen, therefore, that the lethal amount, if there is such a quantity in these cases, is extremely small. Judged by former experience, the amounts deposited in the body as insoluble sulphates sufficient to cause death by production of anemia of the regenerative or aregenerative type, or of necrosis of the jaw from an infection superimposed on a radiation osteitis, ranged from 14 to 180 micrograms. Our contention has always been that if there is enough radioactive substance deposited in the bones to secure photographic impressions in from five days' to two weeks' time, then during life there must have been sufficient radiation from these deposits to cause, in time, exhaustion of the blood-forming centers.

COMMENT

Several features in this case, combined with facts ascertained in a previous study of cases of occupational radium-mesothorium poisoning, have led us to believe that the preexisting deposits of radioactive sub-

2. Flinn, F. B.: A Case of Antral Sinusitis Complicated by Radium Poisoning, *Laryngoscope* 37:341 (May) 1927.



stances in the bones in this case played an important etiologic rôle in the subsequent development of the sarcoma. Of course, this is an alluring theory, which at present is not provable. The arguments for and against it may be summed up, as follows:

1. There was clinical evidence during life, supported by roentgenograms, that peculiar changes existed in the bones long before the appearance of the sarcoma. These were noted chiefly in the head of the right humerus, the acromium and the body of the right scapula and in the scaphoid bone of the right foot. They were of the nature of a radiation osteitis.

2. Microscopic sections of the scaphoid bone, removed at autopsy, showed a lesion that was indistinguishable from the irradiation osteitis produced by heavy external irradiation, as described by Ewing.<sup>3</sup>

3. Anything approaching a sarcomatous transformation in irradiation osteitis due to heavy external irradiation, as seen by radiotherapists, has never been recorded. In fact, the general observation is that the process is more apt to become sclerotic, inactive and acellular.

The effects of single or repeated doses of external irradiation, however, must be quite different from those due to a never ceasing radiation coming from fixed deposits of radium and mesothorium in the bones. Furthermore, in all previously reported injuries of body or tissues as due to radiation and irradiation, the alpha rays never played the important rôle that they did in these cases. Here 95 per cent of the radiation was alpha, which biologically and chemophysically is much more destructive to body tissues than either beta or gamma radiation. In no previous experience have the internal vital organs been constantly exposed to their deadly effect for periods of years; for, in the case of all forms of external therapeutic irradiation, the alpha particle is usually screened or cannot penetrate more than 1 mm. of skin.

4. There was clinical evidence during life, supported by roentgenograms, that the sarcoma started in an area that previously was the seat of a radiation osteitis, while surrounding areas, also the seat of an osteitis, were not affected.

5. It should also be noted that while internal metastases and metastases to the bones were not observed in this case, there was a profound anemia, which at autopsy was shown to be a regenerative, leukopenic anemia, the femurs being filled with dark red marrow. This same type of anemia was found in three other fatal cases among watch dial painters, and was described as due to the effects of constant bombardment of the adjacent blood-forming centers especially by alpha particles.<sup>1</sup> Of course, the same type of marrow has been seen in other

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3. Ewing, James: Radiation Osteitis, *Acta radiol.* 6:399, 1926.

diseases, notably addisonian anemia, and by Ewing<sup>4</sup> in large areas of bone the seat of spontaneous osteogenic sarcoma having nothing to do with radium.

6. The part played by trauma in this case is difficult to determine. Many surgeons would find an adequate cause for the sarcoma in the fall followed by limited motion and pain in the shoulder and the insult of an exploratory operation that did not disclose any pathologic change. We have always been of the opinion that single falls and external violence in the production of osteogenic sarcoma have been greatly exaggerated. They do not offer a satisfactory explanation. Trauma, however, cannot be entirely ignored. In this connection, the remarks of Ewing<sup>5</sup> are of interest: "The idea that trauma, or any other factor, may lead to the development of sarcoma at the ends of long bones which are previously normal, is, I think, without satisfactory foundation. I have examined many cases of supposed traumatic origin and nearly always found that the tumor preceded the trauma. The high proportion of traumatic bone sarcomas reported by some observers seems to be obtained by very uncritical study. The previous integrity of the part can rarely be determined with reasonable certainty, and cannot be assumed on the statement of the biased patient." Kessler,<sup>6</sup> medical director of the New Jersey Workmen's Compensation Bureau, informed us that in 56,000 injuries examined by him, the result of industrial accidents, he observed only nineteen alleged malignant conditions attributed to trauma. Of the nineteen cases, but six were fairly well proved (the compensation law giving the employee the benefit of the doubt). Sarcoma of the bone was found in only one instance.

7. Since the cause of osteogenic sarcoma is unknown, the great majority of cases must be classed as spontaneous in origin. Why is not this case, therefore, of the same origin? Against this assumption is the incidence. Ophüls,<sup>7</sup> in an analysis of 3,000 autopsies, encountered sarcoma of the bone in only two cases, or 0.06 per cent. During the years from 1918 to 1927 inclusive, of 134,500 admissions to the Newark City Hospital (850 beds), only 14 (0.0001 per cent) were for osteogenic sarcoma of a long bone. Primary bone tumors, then, are of unusual occurrence. The incidence of two osteogenic sarcomas in fifteen persons dying as the result of an occupational poisoning by radioactive substances is too high to be mere coincidence.

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4. Ewing, James: Personal communication to the author.

5. Ewing, James: *Neoplastic Diseases*, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 310.

6. Kessler, H. H.: Personal communication to the author.

7. Ophüls, William: *A Statistical Survey of Three Thousand Autopsies*, Stanford University Press, Stanford University, 1926.

8. It is of great importance to radiotherapeutists that they should recognize the possibility of the production of a malignant growth by undue or excessive irradiation. The radiation in these dial painters was unique, in that it was constant over every second of the day for years. In addition, the alpha particle played an important part, never played by it before, according to previous records of the deleterious effects of irradiation. What evidence is there that single or repeated interrupted exposures to x-rays or radium produce malignant changes in the tissues? With the exclusion of many reports of epitheliomas that have been engrafted on irradiation dermatitis, which are now becoming rare owing to better protective technic, there still remains evidence in the literature that malignant changes, especially sarcomatous changes, have followed irradiation. Only a few of these instances need be mentioned: A sarcoma following roentgen treatment for joint tuberculosis was reported by Baumann.<sup>8</sup> A sarcoma of the uterus and ovaries following irradiation was reported by Vogt.<sup>9</sup> A sarcoma of a cicatrix after an irradiation dermatitis was reported by Complani,<sup>10</sup> and instances of roentgen sarcoma were recorded by Pforringer.<sup>11</sup>

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8. Baumann, M.: Roentgen Sarcoma After Irradiation for Joint Tuberculosis, *Strahlentherapie* **26**:610, 1927.

9. Vogt, E.: Sarcoma of Uterus and Ovaries Following Irradiation, *Fortschr. a. d. Geb. d. Röntgenstrahlen* **35**:44, 1926.

10. Complani, M.: Sarcoma of Cicatrix Following Radiation Dermatitis, *Radiol. Med.* **14**:841 (Oct.) 1927.

11. Pforringer, S.: Roentgen Ray Sarcoma, *Strahlentherapie* **26**:610, 1927.

## VARIATIONS AND ANOMALIES OF THE VENOUS VALVES OF THE RIGHT ATRIUM OF THE HUMAN HEART\*

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The eustachian valve or valve of the inferior vena cava and the thebesian valve or valve of the coronary sinus are normally both remnants of the right valve of the sinus venosus.

### EMBRYOLOGY

In the embryonic development of the heart, according to the works of His,<sup>1</sup> Born<sup>2</sup> and Röse,<sup>3</sup> the single atrial cavity is divided into its two definitive chambers in the following manner: The septum primum arises from the mid-dorsal wall of the atrium and eventually fuses with the endocardial cushions at the juncture of the atrial and ventricular cavities. A perforation of the septum primum occurs to form the foramen ovale. This is subsequently closed by the fusion of the left valve of the sinus venosus and the septum secundum, which appears in close proximity to the septum primum as an outgrowth from the ventral and the caudal wall of the right atrium (fig. 1).

The right horn of the sinus venosus lags somewhat in its evolution and is taken up in the wall of the right atrium, which causes the opening into the right atrium of the superior and the inferior venae cavae. The right valve of the sinus venosus at one time nearly divides the right atrium into two chambers, but later it becomes progressively lower, its cephalic portion remaining as the crista terminalis, its caudal portion being divided to form the valve of the inferior vena cava (eustachian valve) and the valve of the coronary sinus (thebesian valve). As the left horn of the sinus venosus is migrating across the posterior wall of the atrium during the stage of absorption of the remainder of the sinus, it projects into the lumen of the atrium as the inferior sinus septum and divides the caudal portion of the right sinus valve into these two definitive valves. The opening of the left horn of the sinus venosus is

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\* Submitted for publication, Oct. 8, 1928.

1. His, W.: *Anatomie menschlicher Embryonen*, Leipzig, F. C. W. Vogel, 1885.

2. Born, G.: *Ueber der Bildung der Klappen, Ostien und Schweidewände im Säugetierherzen*, *Anat. Anz.* **3**:606, 1888; *Beiträge zur Entwicklungsgeschichte des Säugethierherzens*, *Arch. f. mikr. Anat.* **33**:284, 1889.

3. Röse, C.: *Beiträge zur vergleichenden Anatomie des Herzens der Wirbelthiere*, *Morphol. Jahrb.* **16**:27, 1890.



the left duct of Cuvier, which is thus pulled over to a place beneath the orifice of the inferior vena cava and persists in part as the coronary sinus. The septum spurium is a vertical ridge formed by fusion of the right and the left valves of the sinus venosus on the dorsal and the cephalic walls of the right atrium, and this is also taken up into the wall of the atrium as it expands. It partly remains, however, to form the uppermost portion of the crista terminalis, where it separates sharply the orifice of the superior vena cava from the atrial appendage.

The eustachian valve serves to direct the blood in embryonic life from the inferior vena cava into the left atrium through the foramen ovale. The thebesian valve possibly serves to prevent regurgitation of the blood into the coronary sinus during auricular systole. This supposition, however, seems unlikely since the thebesian valve is usually incompetent, that is, it is not sufficiently extensive to close the orifice of the coronary sinus, or, if so, is usually fenestrated.

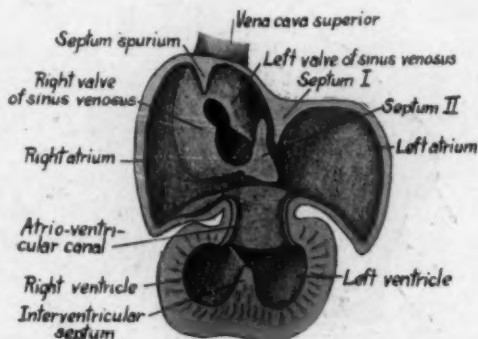


Fig. 1.—Inner view of the dorsal wall of the heart of a 10 mm. human embryo. Drawn from a Ziegler model of one of His' embryos (after Jordan, H. E., and Kindred, J. E.: *Textbook of Embryology*, New York, D. Appleton & Company, 1926).

#### DESCRIPTION OF THE ADULT VALVES

The eustachian valve is usually a muscular and membranous fold in the right atrium extending posteriorly from below the fossa ovalis and then upward just anterior to the orifice of the inferior vena cava, in the upper portion of which it is lost. Its free margin is concave and directed upward and forward; its adherent border is convex and directed downward and backward. One of its surfaces is turned laterally toward the atrium, the other medially toward the vessel. The lower portion is a transverse muscular ridge (the sinus septum) continuous with the limbus fossae ovalis; the upper portion is usually membranous. Often the membranous part of the valve contains thin strands of ordinary cardiac muscle, especially in its attached portion. Often, also, it has fenestrae, and sometimes has thin strands of endocardium attached at two points



along its edge or forming a little network there. The valve is usually not more than 1 cm. wide in the adult. In some cases, the eustachian valve is inconspicuous or entirely lacking. In others, it is broad, projecting far into the right atrium. Sometimes it is thin and flabby, sometimes fibrous and taut.

The thebesian valve is directly below the lower portion of the eustachian valve in the space between this and the edge of the atrioventricular foramen at the juncture of the lower portion of the interatrial septum and the posterior wall of the atrium in close association with the mouth of the coronary sinus, to which it is usually placed laterally. It is frequently semilunar or crescentic with its anterior free edge concave, and its posterior attached edge convex. It is often fenestrated or made up of a network of threads. In fact, its size and form are extremely variable. It may be absent, represented merely by a thin, narrow ridge

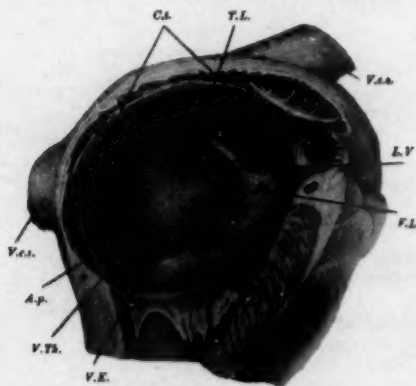


Fig. 2.—Right atrium with the lateral wall removed to show the relationship of the orifices of the atrium and the usual forms of the eustachian and the thebesian valves; *V.E.*, eustachian valve; *V.Th.*, thebesian valve; *A.p.*, auricula posterior; *V.C.I.*, inferior vena cava; *C.A.*, crista terminalis; *T.L.*, tuberculum loweri; *V.C.S.*, superior vena cava; *L.V.*, limbus vieussenii; *F.L.*, Foramin Lannelongeus (after Tandler, Julius, in Bardeleben: *Handbuch der Anatomie des Herzens*, Jena, Gustav Fischer, 1913).

on the posterior edge of the mouth of the coronary sinus, or present as a large membrane completely covering the sinus orifice. It may even be anterior to the orifice, placed obliquely, transversely or vertically across it. Usually, it is thin and translucent. Sometimes there is a definite connection between it and the eustachian valve. The orifice of the coronary sinus with its valve often lies in a saccular depression between the lower portion of the eustachian valve and the atrioventricular rim; this is the appendix auricularis posterior of His or the subeustachian sinus of Keith. Figure 2 shows the most common form of the valves and their relationships in the atrial cavity.

ANOMALIES OF THE VALVES OF THE RIGHT ATRIUM

Anomalies of these valves are dependent on the degree of the regression of the right and the left valves of the sinus venosus, the septum spurium and the sinus septum. Hearts with defective development of the interatrial septum may contain all grades of persistence of these four structures, but the completely developed heart presents relatively few types of anomalies of the valves. In the adult heart, rudiments of the right venous valve are found at the sharp anterior rim of the orifice of the inferior vena cava, extending upward to the upper portion of the crista terminalis and downward across the orifice of the coronary sinus toward the tricuspid orifice. Remnants of the left venous valve are situated on the interatrial septum in the posterior region of the annulus fossae ovalis and the intervenous tubercle (*tuberculum loweri*), which is merely an eminence superior to the fossa ovalis between the orifices of the venae cavae. Residual structures of the septum spurium are found anterior to the mouth of the superior vena cava near the interatrial septum. Remnants of the sinus septum are seen normally in the muscular ridge that extends from the lower end of the limbus fossae ovalis to the inferior part of the rim of the orifice of the inferior vena cava and becomes a part of the normal eustachian valve. If the inferior sinus septum has merely fused with the right venous valve and has not divided it, the eustachian and the thebesian valves are formed as a continuous fold with an attachment to the wall of the atrium in the region of the inferior sinus septum. If the inferior sinus septum has failed entirely, the two valves are seen as a simple membrane or reticulum unattached except perhaps posteriorly to the wall of the atrium.

REVIEW OF THE LITERATURE

So far as I know, a review of the literature regarding these anomalies has never been made.

Lindes<sup>4</sup> described the heart of an infant, in which there was a single atrial cavity and other congenital anomalies. The structures present were similar to those that Ruge,<sup>5</sup> in case 2, interpreted as persistent right and left venous valves.

Maier<sup>6</sup> reported an adult heart in which there were two folds in the right atrium, interpreted by Ruge, in case 13, as a persistent right venous valve and a remnant of the septum primum.

4. Lindes, G.: *Ein Beitrag zur Entwicklungsgeschichte des Herzens*, Inaug. Dis., Dorpat, 1865.

5. Ruge, Hans: *Ueber Defecte des Vorhofsscheidewand des Herzens*, Virchows Arch. f. path. Anat. **126**:323, 1891.

6. Maier, R.: *Zur Casuistik der Herzfehler*, Ber. ü. d. verhandl. d. nat. Gesellsch. **4**:478, 1867.

Schmidt<sup>7</sup> stated that in adults now and then the eustachian valve is lengthened upward to the anterior edge of the superior vena cava, and that sometimes a broad communication exists between the eustachian and the thebesian valves. These forms represent a slight incompleteness of regression of the right venous valve to its final adult vestige as the eustachian and the thebesian valves. These forms are, indeed, not uncommon.

Rokitansky<sup>8</sup> presented two cases of anomalous membranes in the right atrium that Chiari<sup>9</sup> later concluded represented the right venous valve (Rokitansky's case 16) and the left venous valve (Rokitansky's case 17).

Lauenstein<sup>10</sup> described a variation of the valves that he had observed five times in 100 necropsies. In these hearts, the two valves, eustachian and thebesian, which are ordinarily separate, were formed by one extensive membrane. This common valve was a simple membrane in one case, a fenestrated membrane in three cases and a network of exceedingly fine fibers in another case. In one case, it was so large that it divided the atrium into an anterior and a posterior chamber.

Moore<sup>11</sup> reported a case in which there was a large muscular fold beginning just below the fossa ovalis and stretching from the interatrial septum near the orifice of the inferior vena cava to the posterior wall of the right atrium. He described a similar case in another report and stated that he had met with one other example. These were probably much exaggerated eustachian valves with an excessive development of the inferior sinus septum.

Leo<sup>12</sup> described the heart of an infant, in which there were multiple anomalies and an abnormal membrane in the right atrium bounding the orifice of the superior vena cava and a common eustachian and thebesian valve. The interpretation in this case could not be established.

Preisiz<sup>13</sup> reported a case (case 5) of multiple anomalies, among which was a great sievelike flap at the right border of the inferior vena cava

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7. Schmidt: *Bidrag til kundskaben om huerkets udviklingshistorier*, Nord. med. Ark. **2**:1, 1870.

8. Von Rokitansky: *Die Defecte der Scheidewände des Herzens*, Vienna, 1875.

9. Chiari, H.: *Ueber Netzbildungen im rechten Vorhofe des Herzens*, Beitr. z. path. Anat. u. z. allg. Path. **22**:1, 1897.

10. Lauenstein, Carl: *Varietät der Klappen des rechten Atrium*, Virchows Arch. f. path. Anat. **68**:632, 1876.

11. Moore, Norman: *Variety in the Structure of the Heart*, Tr. Path. Soc., London **34**:31, 1883.

12. Leo, Hans: *Ueber einen Fall von Entwicklungshemmung des Herzens*, Virchows Arch. f. path. Anat. **103**:503, 1886.

13. Preisiz, Hugo: *Beiträge zur Lehre von den angeborenen Herzanomalien*, Beitr. z. path. Anat. u. z. allg. Path. **7**:245, 1890.

and the coronary sinus, which, according to Ruge, in case 17, corresponded to the right venous valve.

Stadler<sup>14</sup> reported a case of multiple anomalies of the heart in which there was a fold arising from the inferior vena cava and another passing from the inferior vena cava on the right to the inferior and posterior end of the incompletely developed interatrial septum. Ruge, in case 9, and Chiari both interpreted the first fold as a remnant of the right venous valve and the second as the persistent horizontal ridge developing in embryonic life between the inferior vena cava and the coronary sinus (sinus septum).

Przewoski<sup>15</sup> wrote concerning anomalous chordae tendineae in the heart of man and described networks of fibers near the mouths of the great veins in the right atrium and along the limbus fossae ovalis. He believed these to be remnants of the venous valves of the embryo. His interpretation antedated Chiari's more detailed and precise description and explanations.

The most interesting anomaly of the eustachian valve is that described by Chiari<sup>9</sup> and known since as "Chiari's network." This consists of a network of fine or coarse fibers in the right atrium, its attachments extending from the interatrial septum or the upper portion of the crista terminalis to the thebesian and the eustachian valves or to the region of the orifices of the coronary sinus and the inferior vena cava. Chiari reported eleven cases, in one of which the network was responsible for the death of the patient, a young man aged 24. In this case, there was extensive pulmonary embolism, the source of which was apparently a small thrombus lodged in the confluence of the fibers of the network. Chiari concluded that the malformation represented the remains of the septum spurium and the right venous valve. None of Chiari's cases showed any other relevant congenital anomalies except an additional case of a related anomaly. The heart in this case retained large remnants of both the right and the left venous valves. Chiari called attention to the fact (as shown by Born in mammals and by Röse in monotremes and marsupials) that in these animals the venous valves persist partly or entirely. He stated that Born had also noted that in new-born human beings a semilunar ridge is often to be found under the anterior rim of the opening of the superior vena cava at the juncture of the anterior and the medial walls of the right atrium, which according to its position and

14. Stadler, O.: Ueber eine seltene Missbildung des Herzens, Verhandl. d. phys.-med. Gesellsch. **24**:61, 1890-1891.

15. Przewoski, E.: Anomaliae chordae cordis humani; valvule venae cavae superioris, Pam. Towarz. Lek. Warszaw **92**:400, 1896; Cystenförmige Veränderung der Semilunarklappe der Aorta; Phlebolith des rechten Vorhofes; Sinus venosus fossae ovalis (abstr.), Centralbl. f. allg. Path. u. path. Anat. **8**:152, 1897.



direction is considered a remnant of the free edge of the septum spurium, a trace of which is sometimes recognized even in adults.

A. Weber<sup>16</sup> described a remarkable example of Chiari's network. Besides the main network there was a network of filaments along the posterior edge of the membranous portion, some of the filaments hanging free and supporting a small secondary membrane. Weber interpreted the main network as being derived above from the right venous valve and below from the inferior sinus septum, the upper portion corresponding to the eustachian valve, the lower to the thebesian. He believed that in Chiari's cases, also, the lower attachments of the network were remains of the inferior sinus septum and not displacements of the right venous valve. He referred to the work of Milne-Edwards, which showed that, in certain adult birds, the sinus portion of the right atrium is separated by fleshy strands from the atrial portion proper. The smaller network, he believed, represented remains of the left venous valve.

Swan<sup>17</sup> reported, as an example of Chiari's network, a valvelike flap of endocardium lying against the fossa ovalis on the right side and attached to the annulus fossae ovalis by anastomosing bands closely resembling chordae tendineae. This is certainly not Chiari's network but probably a remnant of the left venous valve which did not completely fuse with the septum secundum. Minor degrees of this anomaly are not infrequent, as noted by Lower, A. Weber, Oppenheimer, Möllendorf and others.

Le Count<sup>18</sup> recorded an instance of Chiari's anomaly, in which the network was entirely below the orifice of the inferior vena cava.

Looser<sup>19</sup> presented an example of Chiari's network, in which there was a thrombus about 2 cm. in diameter attached to a few fibers of the net. A hemorrhagic embolic infarct was present in the left lung, and also thrombi in both femoral veins, so that it was impossible to determine whether the thrombus on the network developed primarily at that site or had been carried there from the venous thrombi and had grown to its final size. Looser considered that these networks may be remnants of the right venous valve, the left venous valve, the septum spurium or the sinus septum. He stated that rudiments of the right venous valve should be looked for at the thebesian valve, the upper part of the eustachian valve and the crista terminalis; remnants of the left venous valve should

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16. Weber, A.: Formation réticulée de l'oreillette droite et fosse ovale anormale d'un coeur humain adulte, *Bibliog. anat.* **6**:17, 1898.

17. Swan, J. M.: Fenestration of the Right Auricle, *Proc. Path. Soc.* **2**:71, 1898-1899.

18. Le Count, E. R.: Network Formations in the Right Auricle, with Demonstration of a Specimen, *Tr. Chicago Path. Soc.* **5**:309, 1901-1903.

19. Looser: Ueber die Netzbildungen im rechten Vorhofe des Herzens, *Inaug. Dis., Zürich*, 1902.



be looked for at the interatrial septum in the arched line which connects the left borders of the two venae cavae, and vestiges of the septum spurium anterior and medial to the mouth of the superior vena cava near the interatrial septum. Fairly large remnants of the right venous valve are by far the most common, those of the left venous valve are more rare, and any notable remnant of the sinus septum is unusual. Looser disagreed with Chiari, maintaining that the latter's eleven networks were all remnants of the right venous valve without any involvement of the septum spurium. He recognized the anomaly in which the eustachian and the thebesian valves are replaced by a common reticulum owing to a lack of fusion of the right venous valve with the sinus septum, which normally becomes the lower part of the eustachian valve and separates this from the thebesian valve. Remnants of the right venous valve are sometimes found at a greater or less distance from their normal site, probably because of irregularities in the growth of the endocardium. A relatively common displacement is that of the threads from the crista terminalis toward Lower's tubercle. The cause of this displacement is probably the proximity of the mouths of the large veins and a distortion of the endothelium during the rapid growth of the heart. There are many transitions from the normal condition of the eustachian valve and the thebesian valve to these reticulate structures.

Ebbinghaus<sup>20</sup> reported a case of Chiari's network and accepted Chiari's explanation.

A. Weber<sup>21</sup> discussed the question of remnants of the left venous valve as commonly seen. At the postero-inferior part of the fossa ovalis are frequently found punched-out areas beneath which a little probe can be moved a variable distance over the subjacent endocardial surface. This space passes anteriorly into the fossa ovalis and posteriorly toward the inferior vena cava. It is the part of the fossa ovalis that lacks the projecting limbus. Weber interpreted this perforated portion as a remnant of the left venous valve, the space beneath representing the inter-septovalvular space of Röse. The left venous valve fuses not only with the septum secundum to form the limbus of the ostium secundum but also directly with the septum primum anterior to the posterior rim of the septum secundum. Weber quoted Grosser as having found a persistence of the left venous valve in a certain number of *Cheiroptera*, and Devez in the American *Didelphys*. The echidna (monotreme) has a valve for each vena cava and a valve common to both. The ornithorynchus has a common internal valve represented by a simple musculomembranous

20. Ebbinghaus, H.: Zur Kasuistik der kongenitalen Herzfehler und deren möglichen Folgen, München. med. Wchnschr. 51:797, 1904.

21. Weber, A.: Restes de la valvule veineuse gauche dans le coeur humain adulte, Bibliog. anat. 13:11, 1904.

ridge. Other animals having an internal valve in the inferior vena cava are *Myrmecopha tetradactyla*, the jaguar and the cabai.

Wortmann<sup>22</sup> described an infant's heart presenting many unusual anomalies. In place of the eustachian valve, there was a bulging, sac-like membrane, at one edge of which was attached a spherical, blackish thrombus, "the size of a small pea." There was also an independent network along the left edge of the orifice of the inferior vena cava with threads attached to Lower's tubercle. The saclike membrane was a residuum of the right venous valve, the network a remnant of the left venous valve.

In Thilo's Inaugural Dissertation,<sup>23</sup> in 1909, were descriptions of five cases of reticula in the right atrium, two of which were similar to Chiari's first four cases. In one of these, a grayish-red, "pea-sized," spherical thrombus was attached to the network. There was an embolic infarct of the lung, and also a thrombus in the common iliac vein, so that the source of the pulmonary thrombus may have been from this and not from the thrombus of the reticulum.

Lesieur, Froment and Crémieu<sup>24</sup> reported an instance of an "anomalous thebesian valve associated with a large patent foramen ovale." They believed the flap to be a remnant of the left venous valve which had failed to fuse with the septum secundum to close the foramen ovale.

Möllendorff,<sup>25</sup> described a heart containing remnants of both the right and the left venous valves. The sinus septum had not divided the right venous valve into its two definitive valves.

Haas<sup>26</sup> reported an unusual case. There were three groups of threads forming a network and replacing the eustachian and the thebesian valves. The uppermost group was attached to the region of the crista terminalis beside the right edge of the superior vena cava. On the net hung an embolus 6 cm. long and surrounded twice in its middle by a thread. This embolus had undoubtedly come from a thrombus in the left femoral vein and had become ensnared in the network, thus preventing fatal pulmonary embolism.

22. Wortmann, W.: Ueber eine seltene Herzmissbildung. Zugleich ein Beitrag zur Frage der Netzbildungen im rechten Vorhofe, Inaug. Dis., Würzburg, 1909.

23. Thilo, L.: Zur Kenntnis der Missbildungen des Herzens, Inaug. Dis., Leipzig, 1909.

24. Lesieur, C.; Froment, J., and Crémieu, R.: Coexistence d'une communication interauriculaire et d'une anomalie de la valvule de thébésius, *Lyon méd.* **116**:1045, 1911.

25. Von Möllendorff, Wilhelm: Ueber abnorme Erhaltung der Sinuskappen im rechten Vorhof eines menschlichen Herzens, *Anat. Anz.* **40**:406, 1912.

26. Haas, W.: Ueber einen weiteren Fall von Netzbildungen im rechten Vorhof mit einem in denselben verfangenen Embolus, Inaug. Dis., Karlsruhe, 1916.

F. P. Weber<sup>27</sup> redescribed Ebbinghaus' case, in which he had seen the heart, and reported two of his own. He considered these to be examples of Chiari's network, but they were probably merely exaggerated "openwork" eustachian valves.

Jordan's two cases<sup>28</sup> were good examples of Chiari's network. He mentioned a third case seen two years before. Jordan's conclusion was: "As these bands arise from the interatrial septum in the region developed from the left valve of the sinus venosus and also from the crista terminalis which is the remains of the cephalic portion of the right valve of that sinus and as they insert in close proximity to and directly on the thebesian and eustachian valves it seems that Chiari's explanation is proper. However, the left valve of the sinus venosus is also involved." Jordan noted that both the patients had auricular fibrillation at the time of death, and he speculated as to the rôle the network might play in producing this arrhythmia because of a "close relationship between the network and the conducting system."

Wurm<sup>29</sup> reported a case of corrected transposition of the great vessels and described a network in the left side of the right atrium which he called an instance of Chiari's network. This type of reticulum is not similar to Chiari's cases, however, and such threads are not extremely rare.

#### METHOD OF OPENING THE HEART

I have studied the eustachian and the thebesian valves in 120 hearts collected as a routine. In order to preserve the eustachian valve intact it was necessary to modify the technic of opening the heart.

In a heart opened in the usual routine manner, the eustachian valve is cut almost directly through its middle by the scissors, as they pass between the orifices of the two venae cavae. If the valve is flimsy, as it often is, its two halves collapse against the wall of the atrium and are not seen unless special notice is taken of them. When it is desired to examine the valves, one may first look through the open end of the inferior vena cava into the right atrium, and, should an anomalous valve be observed, one may then open the right atrium by an incision anterior and parallel to the anterior rim of the inferior vena cava and then across to the tip of the atrial appendage from the lower end of this opening. This method gives ample exposure of the interior of the right atrium and also preserves the sino-auricular node should the examiner desire to study this microscopically. In removing the heart from the body, care must be taken, in cutting the inferior vena cava, not to encroach on the right atrium.

27. Weber, F. P.: Interesting Cases in Which a So-Called Chiari's Net Was Found in the Right Auricle of the Heart, with or without the Presence of any other Congenital Cardiac Abnormality, *Internat. Clin.* **3**:43, 1920.

28. Jordan, W. R.: Two Cases of Chiari's Network, *Arch. Path.* **2**:840 (Dec.) 1926.

29. Wurm, H.: Angeborener Herzfehler mit "korrigierter" Transposition der grossen Gefässe, *Virchows Arch. f. path. Anat.* **263**:123, 1927.

VARIATIONS OF THE ADULT VALVES<sup>30</sup>

The structure of the eustachian valve varies, but it takes relatively few forms. In the 120 hearts studied with special emphasis on these valves, the eustachian valves could all be classified as of one or the other of six anatomic types. In several hundred other hearts observed later, all of the valves conformed to one or the other of these types. A brief description of each type of valve with the relative number of hearts in which it was found, follows.

1. The valve absent (seventeen cases). The sinus septum and the anterior rim of the inferior vena cava were all that denoted the previous existence of a right venous valve, except for the thebesian valve, which was present in sixteen cases and absent in one case.

2. A simple nonfenestrated flap or membrane (sixty-nine cases). The usual form was crescentic. It varied from a narrow little fold along the anterior edge of the orifice of the inferior vena cava, to a broad membrane 2.3 cm. wide. The valve, in some cases, was a thin, flabby, transparent membrane distinct from the rim of the vena cava, and in some cases it was a tough, taut fold merging with the rim of the vena cava and the wall of the atrium. It sometimes had muscle fibers in it, especially thin, narrow strands near the attached edge.

3. A fenestrated semilunar membrane containing from one to many fenestrae (twenty-two cases). In one of the cases, it had accessory threads on its surface. In most of the cases, the valve was thin. Sometimes it was narrow or broad and veil-like.

4. A valve formed in part or entirely of a network of threads (seven cases). In some of the cases this looked like a cobweb.

5. Both the eustachian and the thebesian valves formed of one membrane (two cases). In one case the transverse sinus septum was lacking.

6. Chiari's network (three cases). One other instance of Chiari's network was found in a preserved heart.

Of the 120 hearts, twelve had definite connecting tissue between the eustachian and the thebesian valves. The average width of the simpler forms was 0.35 cm. and the average length at the free edge 3.42 cm. The minimal width was 0.15 cm. and the maximal 2.3 cm. The minimal length at the free edge was 1.7 cm. and the maximal 7.5 cm.

The thebesian valve varied anatomically more than the eustachian. The thebesian valves in these hearts may be classified as follows:

1. The valve absent (thirteen cases). The coronary sinus opened directly into the atrial cavity.

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30. All descriptions and measurements of the valves are given as for a heart held with the long axis vertical, the observer looking at the right side of the interatrial septum.



2. A simple nonfenestrated fold attached to the posterior edge of the orifice of the coronary sinus (sixty cases). This varied from a narrow little rim to a broad membrane extending over the sinus orifice. The predominating shapes were crescentic, semilunar and triangular. The valve was usually thin.

3. A simple fenestrated membrane (seventeen cases). This type varied from a thin crescentic flap to a large fold covering the orifice.

4. A rather simple fold with one or more accessory threads (seven cases).

5. A simple vertical bar (two cases).

6. A valve consisting of fine threads only (four cases). In two of the cases, the threads formed a network in the sinus orifice. In one, a thread ran obliquely across the orifice.

7. A U-shaped fold with the sinus orifice between the limbs (five cases).

8. A valve represented by complicated membranes passing vertically across the sinus orifice (four cases).

9. The thebesian and the eustachian valves formed by one fold (two cases). In one of these cases, the transverse sinus septum was lacking.

10. Miscellaneous type (six cases): (a) an inverted U-shaped fold with the sinus orifice between the limbs; (b) a crescentic fold with strands anterior to the sinus orifice; (c) a crescentic fold with a branch; (d) a network over the sinus orifice; (e) a large, fenestrated veil in the sinus orifice with anchoring strands, and (f) a triangular fold with one fenestra, attached to the inferior rim of the sinus orifice.

Only three or at most four of these valves may be considered at all competent, that is, sufficient to close the orifice against a backflow. The average horizontal width of the simpler forms of these valves was 0.6 cm. and the average vertical width 1.05 cm. The minimal horizontal width was 0.05 cm. and the maximal 2.2 cm. The minimal vertical width was 0.6 cm. and the maximal 2 cm.

In another series of hearts from fifty adults, the thebesian valves were of somewhat similar types:

1. The valve absent (five cases).

2. A simple nonfenestrated fold attached to the posterior edge of the orifice of the coronary sinus (twenty-six cases).

3. A simple fenestrated membrane (nine cases).

4. A crescentic fold with accessory threads anteriorly (two cases).

5. A simple vertical bar (two cases).

6. A simple horizontal bar (two cases).

7. Miscellaneous types (four cases): (a) fenestrated vertical membrane anterior to the sinus orifice with a strand across the sinus orifice



to the posterior rim of the orifice; (*b*) a network with an accessory thread anterior to the sinus orifice; (*c*) a large, horizontal, fenestrated membrane in the sinus orifice extending far out anteriorly, with anchoring strands to the sinus inferiorly, and joining the eustachian valve at its posterior end, and (*d*) a membrane stretching obliquely across the sinus orifice with a vertical branch anterior to the orifice.

The average horizontal width of those valves that could be measured was 0.78 cm. and the average vertical width 1.03 cm. The minimal horizontal width was 0.15 cm. and the maximal 2.3 cm. The minimal vertical width was 0.6 cm. and the maximal 2 cm.

The simplest forms of the eustachian valve are usually associated with the simplest forms of the thebesian valve. When one is fenestrated the other is usually fenestrated also.

From this series of hearts, with the addition of a few other specimens, one can select a number of cases which illustrate a gradual progression from unusually large but structurally normal valves to those valves which show features due to some embryologic deviation. The group of hearts to be described includes all the types of anomalies that have been described in connection with the venous valves of the right atrium in the adult structure.

#### REPORT OF CASES

CASE 1.—The eustachian valve was a large, tough, fenestrated semilunar membrane, 3.5 cm. long at its free edge and 1.5 cm. broad at its greatest width (fig. 3). Muscle strands were not visible macroscopically. Seen through the orifice of the inferior vena cava from without, the valve seemed almost to cover the orifice of the vein. The thebesian valve was similar, but much thinner, and the fenestrae were proportionately larger. There was nothing especially remarkable about these valves. They merely represented the more exaggerated type of the usual form.

CASE 2.—The eustachian valve was an openwork, fibrous, white structure (fig. 4), which, in its upper and posterior portion, consisted of interlacing fibrous threads and strands. The free margin of the valve was 2.5 cm. long and the greatest width measured 1.5 cm. If, instead of the fibers, this valve had contained more membrane, it would have closely resembled the valve in case 1. The thebesian valve was a simple semilunar fold.

CASE 3.—The eustachian valve was a large, flabby, thin, white and much fenestrated veil-like membrane. The free edge measured 5 cm. and the greatest width 2.3 cm. The thebesian valve was a large, nonfenestrated fold immediately below and almost continuous with the eustachian valve. It completely covered the orifice of the coronary sinus. The two valves together constituted a large remnant of the right venous valve of the embryo, but conformed to the type of valves found in adults.

CASE 4.—A woman, aged 65, died of congestive heart failure due to hypertension. The electrocardiogram revealed auricular flutter with an auriculoventricular block, shifting back and forth between 2:1 and 4:1 ratios, and an incomplete right bundle branch block with a QRS interval of 0.12 second. The heart weighed 684 Gm. The eustachian and the thebesian valves were formed by a continuous,

large, fenestrated membrane extending from below the orifice of the coronary sinus upward in front of the inferior vena cava to a broad attachment in the roof of the right atrium about 1.2 cm. posterior to the median portion of the crista terminalis. This membrane was attached to the usual transverse muscular ridge that lies between the inferior vena cava and the coronary sinus (a remnant of the inferior sinus septum) and forms the lower end of the normal eustachian valve. The entire membrane measured 5 cm. at its free edge and 1.6 cm. at its widest part. It was of the type described by Lauenstein. In the nonfenestrated portion of the free edge was a flat band of cardiac muscle, 0.2 cm. wide, which



Fig. 3 (case 1).—The right atrium is opened to show a large, fenestrated, semilunar eustachian valve and a similar thebesian valve. *A* indicates the fossa ovalis, *B* the eustachian valve, *C* the thebesian valve and *D* the tricuspid valve.

was continuous with the musculature of the atrium above and with that of the transverse ridge below. Such a distribution of muscle raises the question whether the ring of muscle thus formed could have been the pathway of the simple circus movement of auricular flutter.

CASE 5.—A man, aged 33, had been subject to chronic mitral endocarditis and auricular fibrillation. He died of congestive heart failure. The weight of the heart was 707 Gm. Both atria were greatly dilated, both ventricles greatly hypertrophied and the mitral orifice thickened, rigid and stenotic. The venous valves

were of the type described by Lauenstein, but the inferior sinus septum had failed to unite with the right venous valve. The two valves were a continuous thin membrane with a thin bridge between them (fig. 5). This bridge formed an arch over the orifice of the coronary sinus, and the membrane was not attached to the wall of the atrium in the region of this arch. Both the upper and the lower portions of the common valve were expanded, somewhat triangular and fenestrated, and lay in different planes. Above, the valve was attached to the wall of the atrium just anterior to the lower half of the orifice of the inferior vena cava;



Fig 4 (case 2).—The right atrium is opened to show a large, openwork eustachian valve. *A* indicates the orifice of the inferior vena cava, *B* the eustachian valve, *C* the orifice of the coronary sinus and *D* the thebesian valve.

below, it fused with the endocardium by a wide base anterior to the orifice of the coronary sinus and a short distance above the tricuspid orifice.

CASE 6.—In this case, also, the two valves were united in one large membrane. The transverse muscular ridge (sinus septum) was present but was connected with the common valvular fold by a little thread only. There was also a network on the posterior half of the fossa ovalis attached along the posterior rim of the limbus and by short bands to the endocardium covering the fossa ovalis (fig. 6).

CASE 7.—A man, aged 69, died from bronchopneumonia, following colostomy for carcinoma of the descending colon. In the left pulmonary artery was a fairly large antemortem thrombus. The heart did not show anything of note except the venous valves. There was a small, triangular membrane flanked by a thread on each side, which arose from the upper and anterior part of the rim of the orifice of the inferior vena cava (fig. 7). The small membrane and threads



Fig. 5 (case 5).—The lower interior of the right atrium is exposed to show a combination of the eustachian and thebesian valve with absence of the inferior sinus septum.

quickly converged to be lost in the substance of a firm white thrombus, which was irregularly round with excrescences above and below. The thrombus measured 1.3 by 0.8 by 0.8 cm. From the lower end of the thrombus, some closely entwined threads emerged and passed downward and posteriorly. They were attached by a triangular membranous and filamentous base to the anterior rim of the inferior vena cava, the distance between the upper end of the upper attachment and the

lower end of the lower attachment on the rim of the vena cava being 2.7 cm. From the lower part of the entwined threads below the thrombus, a thread 2.8 cm. long passed downward and was attached to the anterior edge of an extensive fenestrated thebesian valve, measuring 1.2 by 1.1 cm., which covered the orifice of the coronary sinus. Another shorter thread arose from the inferior sinus septum and passing downward was attached with this longer thread to the thebesian valve.



Fig. 6 (case 6).—An exposure as in figure 5. The large common fold of the eustachian and the thebesian valves has been pulled to the side to show the network on the posterior half of the fossa ovalis (the network is held taut by one cotton thread, *x*).

CASE 8.—The heart appeared normal. The eustachian valve was a thin, triangular, fenestrated membrane with its base attached to the lower portion of the rim of the inferior vena cava and the inferior sinus septum. Its base was about 2 cm. long, and the distance from the middle of the base to the apex, when the membrane was held taut, was about 2 cm. From the apex, a thin thread passed obliquely across the atrium and upward to be inserted on the interatrial septum just above the tuberculum loweri about 1.5 cm. posterior to the crista terminalis.



This thread was 3.5 cm. long. The thebesian valve was a large thin membrane, covering the orifice of the coronary sinus and attached to its rim by threadlike processes. The orifice and the valve lay in a deep recess beneath the inferior sinus septum, the subeustachian sinus of Keith.

CASE 9.—The heart did not play a part in the patient's death and appeared normal. There was a large, delicate, fenestrated and netlike eustachian valve attached to the rim of the inferior vena cava except in its upper portion. The free edge was about 4 cm. long and the greatest width was about 1.3 cm. From the upper portion of the valve, two threads were given off close together and ran across the orifice of the inferior vena cava to be attached close together to the tuberculum loweri just above the limbus fossae ovalis. They were about 2 cm.



Fig. 7 (case 7).—The wall of the right atrium is removed to show an antemortem thrombus formed about the fibers of a reticular eustachian valve.

long. The thebesian valve was a large membrane similar to the eustachian valve, covering the orifice of the coronary sinus.

CASE 10.—The heart did not play an important part in the history of this case. A cobweb-like network of thin, delicate fibers in front of the orifice of the inferior vena cava extended partially across the atrium. A thin, narrow membrane represented the usual form of eustachian valve, and the threads of the network were largely attached along the course of this; but, for the most part, they were inserted directly into the rim of the inferior vena cava, anterior to the attachment of the valve (fig. 8). In the upper part they were attached to the upper part of the rim of the inferior vena cava, independent of the eustachian valve, which ended considerably below this part. One delicate thread, about 5 cm. long, left the anterior edge of the network and ascended to the roof of the atrium, where it was attached

about 1 cm. posterior to the crista terminalis. The whole network was flaccid. The thebesian valve was a small, thin, fenestrated semilunar membrane.

CASE 11.—A man, aged 40, died suddenly of pulmonary embolism while undergoing examination at the clinic. He had been operated on elsewhere for a strangulated hernia a year before, and had suffered from weakness, abdominal pain, dyspnea and swelling of the legs at night since that time. The clinical examination revealed, besides other things, an indefinite mass in the abdomen, marked edema of the left arm up to the shoulder and edema of both legs. There



Fig. 8 (case 10).—The right atrium is opened to show a cobweb-like network in connection with the eustachian valve and a long thread passing from it across the cavity to the roof. *A* indicates the crista terminalis, *B* Chiari's network, *C* the orifice of the inferior vena cava, *D* the eustachian valve, *E* the thebesian valve, and *F* the tricuspid valve.

was a suggestion of acromegaly in an increased prominence of the malar bones and the large square hands. Necropsy revealed massive pulmonary embolism and thrombosis of the left innominate and the subclavian veins, and of the common iliac and the right iliac veins. The hypophysis was enlarged to three times its normal size, and microscopically revealed carcinomatous invasion. A portion of the ileum was black and edematous, with stenosis of the lumen, evidently representing an old healed gangrene of the bowel from the time of the strangulation

of the hernia. The heart was essentially normal except for the condition in the right atrium (fig. 9). Evidence of a eustachian valve or of any remnant of the inferior sinus septum was absent. The orifice of the coronary sinus was 1.3 cm. wide in the collapsed state; a thebesian valve was not present. Across the atrial cavity from the region of the orifices of the inferior vena cava and the coronary sinus, several delicate threads passed to an insertion into a wide, flattened and extensive crista terminalis just anterior to the orifice of the superior vena cava.



Fig. 9 (case 11).—The right atrium is opened to show the eustachian and the thebesian valves replaced by a Chiari's network (photograph retouched).

There were three main threads, all more than 6 cm. long, which were difficult to trace from insertion to insertion because of an entanglement in their median portions. Above, these threads were attached about 1 cm. apart, in a row, to the crista terminalis by little cone-shaped bits of endocardium. After leaving the entanglement, which was about 1.5 cm. long, they became several small threads, which were attached below to the wall of the atrium in front of and above the orifice of the coronary sinus. Near the end of an unattached thread was a small discoid antemortem thrombus about 0.4 cm. in diameter and 0.15 cm. thick.

## COMMENT

This series of cases progresses from the more exaggerated forms of the usual type of eustachian and thebesian valves to those in which the valves have been replaced by a number of threadlike processes. Cases 1, 2 and 3 are instances of large fenestrated forms without accessory threads and with the usual ridge representing the remains of the inferior sinus septum. Case 4 illustrates the incomplete separation of the two valves by the inferior sinus septum. Case 5 is an example of a complete failure of the inferior sinus septum, the two valves being one membrane uninterrupted by the muscular ridge. In case 6, the sinus septum was present but failed to cleave the right venous valve into its two definitive valves. The network in the fossa ovalis was a remnant of the left venous valve, which had failed to unite completely with the septum secundum. Case 7 showed a network of threads, one of which passed downward from the eustachian network to connect with the large fenestrated thebesian valve. In case 8, a single strand passed from a much fenestrated anomalous eustachian valve to be attached to the interatrial septum. In case 9, two threads passed from the eustachian valve network to the tuberculum loweri. A single long fiber, 5 cm. long, in case 10, left the cobweb-like eustachian valve network, passed across the atrium and was inserted into the roof of the chamber. Case 11 was the most aberrant form of all, both eustachian and thebesian valves being replaced by a number of long threads stretching completely across the atrial cavity from the region of the orifices of the inferior vena cava and the coronary sinus to the upper part of the crista terminalis. In not one of these cases was there any other cardiac anomaly. These last four cases fall readily into the class described by Chiari, since they have threadlike processes formed in association with the venous valves and inserted on remote unnatural parts of the wall of the atrium.

In the main, most authors have agreed on the interpretations of these anomalies of the valves. There are a few cases in which a difference of opinion might exist, but I feel that interpretations of cardiac anomalies are not worth much unless the interpreter has the condition well visualized or has access to the heart itself.

Concerning the cases designated Chiari's network, there are two main conceptions. Chiari concluded that the reticulum is a remnant of the right venous valve and of the septum spurium. Looser believed that it is formed entirely by the right venous valve and a dislocation of the fibers from their normal site by irregularities in the growth of the endocardium. Jordan wished to include the left venous valve as playing a part in the formation of the reticulum. I consider Looser's explanation as the one nearer the truth, preferring to look on all folds or networks formed in association with or replacing the eustachian and the thebesian

valves as remnants of the right venous valve with or without involvement of the inferior sinus septum. Additional evidence for the theory that a dislocation of fibers may occur in the formation of these reticulated structures is the attachment, in some cases, of fibers of the lower part of the network at points in the right atrium far below the lower limit of the right venous valve. This is exemplified best, perhaps, by Chiari's case 10. Spurious threads are seen more rarely in the left atrium, and are probably due to dislocations of remnants formed usually from the septum primum or even the septum secundum. These structures were recently reviewed by Kleine.<sup>31</sup> This conception limits the remnants of the left venous valve to those threads, networks or loose folds at the edge of the fossa ovalis and mainly in the posterior part, instances of the occurrence of which, in a small way, are frequently seen. Remnants of the septum spurium are then left as the rarest of all and, so far as I know, are limited to those hearts that show a definite semilunar ridge projecting under the anterior rim of the opening of the superior vena cava at the juncture of the anterior and the medial walls of the right atrium. Born is the only author who called special attention to such a ridge, which is seen most often in infants. Anomalies of the sinus septum are also rare as a distinct entity.

This explanation of the origin of Chiari's structure confuses the criteria on which to call a certain reticulum an instance of Chiari's network. Formations of network of the eustachian and the thebesian valves are not uncommon, as shown by the study of the valves in more than 120 hearts. In all of Chiari's cases, however, some of the fibers of the net had their attachment to the atrial wall near the upper portion of the crista terminalis or to the interatrial septum on or near the tuberculum loweri. Therefore, the term, Chiari's network, should probably be applied only to reticular formations that possess such threads.

Clinically, these reticula are usually not of consequence. Instances are on record, however, in which thrombi were found in the reticulum. Five of these have already been noted from the literature, and in Chiari's case 1 such a thrombus apparently caused the death of the patient from pulmonary embolism. Also, in case 11 (fig. 9) of the present series, the patient died of pulmonary embolism, but there was extensive thrombosis of several large veins, as well as the thrombus attached to the network. In case 7 (fig. 7) there was an embolus in the left pulmonary artery, although the patient did not die of pulmonary embolism. The large thrombus surrounding the threads of the eustachian valve was the only source found for the embolus. In another case (not recorded

31. Kleine, H. O.: Zur Morphologie der Missbildungen des linken Vorhofs (Chorda tendinea spuria atrii sinistri), Virchows Arch. f. path. Anat. **267**:281, 1928.



here), the patient died of septicemia following an induced abortion. She had had dyspnea for two years. At necropsy, a large egg-shaped fibromyxoma was found attached to the wall of the left atrium and filling it; on a thread of the eustachian valve was a large recent thrombus. In a fourth case (not recorded here), there were antemortem thrombi on several threads of the thebesian valve. These long threadlike processes hanging limp in the cavity of the right atrium and being whipped about by the blood current must form excellent bases for the formation of thrombi, when the rate of circulation is depressed or the condition of the blood becomes favorable for clotting. That they are whipped about rigorously is shown by cases 7 and 11, in which the threads were so entwined and entangled as to be inseparable for some distance. In Haas' case, instead of being the source of pulmonary embolism, however, the network prevented such a condition by catching a large embolus in its course from the inferior vena cava to the pulmonary artery. The reticulum in one of Thilo's cases may have played a similar rôle, but because of the uncertainty of this I have included it as an instance of the formation of a thrombus *in situ*.

Case 4 of this series illustrates the possible mechanism by which circus movement may ensue in isolated instances. The cardiac muscle bands in the large valvular fold joined with the muscle of the atrium at each end of the fold and thus formed a circuit of muscle about the mouth of the inferior vena cava. The patient had auricular flutter, and it is conceivable that the main path of the contraction wave was this ring of aberrant muscle.

#### SUMMARY

Several varieties of remnants of the venous valves of the embryo occur. There are two main groups of anomalies, those with and those without defective interatrial septums. I have described those without a defective septum.

The literature contains reports of twenty-two acceptable examples of that anomaly known as Chiari's network, including Chiari's original eleven cases. To these I have added four more. The designation, Chiari's network, should be confined, probably, to those reticula in connection with the eustachian and the thebesian valves which have threads attached in the upper region of the atrium, near the crista terminalis, or to the interatrial septum in the region of the tuberculum loweri.

Such reticular formations as have been described are usually not of clinical significance. In a certain number, however, an increased facility for the formation of thrombi on the threads of the network is noted. In the literature, five instances are recorded in which such thrombi were

present, and in one there was no doubt that the thrombus was the cause of fatal pulmonary embolism. In this series were four cases in which thrombi were found in connection with the eustachian or the thebesian valve, all apparently antemortem thrombi. It is possible for a person to succumb to pulmonary embolism the source of which is a thrombus formed on one of these networks. Paradoxically, such a network, by ensnaring an embolus from some vein, may prevent fatal pulmonary embolism.

A theoretical point to be considered is the possible relationship of these networks to auricular fibrillation or auricular flutter.

## LEUKOCHLOROMA IN THE COMMON FOWL

ITS RELATION TO MYELOGENIC LEUKEMIA AND ITS ANALOGIES TO  
CHLOROMA IN MAN \*

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Among the early reports in the literature on the occurrence of a myeloid neoplasm in the common fowl are those published in 1908 by Ellerman and Bang.<sup>1</sup> Their studies at that time were concerned chiefly with efforts to transmit the disease and not with its microscopic changes. From 1915 to 1916, Schmeisser<sup>2</sup> conducted similar transmission experiments with a tumor that was evidently of myelogenic origin. In 1915, Pentimalli<sup>3</sup> published a brief description of two cases of neoplastic growths that he classified as myelocytomas. The first occurred in a hen into which he had transplanted a chondroma. He apparently considered that there had been a "transformation" of the chondroma into the myelocytoma. This explanation did not obtain for the second case.

The myeloid neoplasm in man, commonly known as a chloroma, has been the subject of considerable study. Burns<sup>4</sup> (1823) is credited with making the first observations on it. Dock<sup>5</sup> presented evidence of a relationship between the tumor and leukemia. Dock and Warthin<sup>6</sup> established this point, and called attention to the fact that the bone marrow is the seat of the primary development. In 1910, Lehndorff<sup>7</sup> reviewed the reports of seventy-three cases. From the evidence presented, he classified fifty-six as lymphogenic and seventeen as myelogenic.

\* Submitted for publication, Oct. 15, 1928.

\* From the Veterinary Department, Purdue University Agricultural Experiment Station, Lafayette, Ind., and the Department of Pathology, University of Michigan, Ann Arbor, Mich.

1. Ellerman, V., and Bang, O.: Experimentelle Leukämie bei Hühnern, *Centralbl. f. Bakteriöl.* **46**:4, 595 and 609, 1908.

2. Schmeisser, H. C.: Spontaneous and Experimental Leukemia in the Fowl, *J. Exper. Med.* **22**:820, 1915; Leukemia of the Fowl; Spontaneous and Experimental, *Johns Hopkins Hosp. Rep.* **17**:551, 1916.

3. Pentimalli, F.: Ueber die Geschwülste bei Hühnern, *Ztschr. f. Krebsforsch.* **15-16**:111, 1915-1919.

4. Burns, A.: Observations on the Surgical Anatomy of the Head and Neck, Baltimore, 1823, p. 386.

5. Dock, G.: Chloroma and Its Relationship to Leukemia, *J. M. Sc.* **106**:152, 1893.

6. Dock, G., and Warthin, A. S.: A New Case of Chloroma with Leukemia, with a Study of Cases Reported Since 1893, *Med. News* **85**:971, 1904.

7. Lehndorff, H.: Chloroma, *Ergebn. d. inn. Med. u. Kinderh.* **6**:221, 1910.

The subject was reviewed by Burgess,<sup>8</sup> in 1912, who presented logical reasons for considering the neoplasm as a myelogenic process, and also called attention to the fact that a thorough histologic study had not been conducted on the majority of the growths that had been classified as lymphogenic chloromas. Brannan<sup>9</sup> reviewed seventy-four cases that were reported from 1910 to 1925, of which forty-nine were definitely myeloid in nature. He emphasized the fact that the better studied cases of chloroma had been shown to be of myelogenic origin. Other recent accounts of the disease, with appended bibliographies, can be found in the articles by Boots,<sup>10</sup> Rowe and Hirschboeck<sup>11</sup> and Goodall and Alexander.<sup>12</sup>

Observations by members of the Veterinary Department of Purdue University have shown that from the standpoint of incidence in the common fowl the myeloid tumors rank second in importance to the lymphocytomas. The nature of the lymphocytoma has been thoroughly studied, whereas the myeloid tumors have received but slight attention from the comparative pathologist. The present publication deals with thirty-seven myeloid neoplasms that I studied during the years 1925 to 1928.

#### SYMPTOMS

The clinical manifestations in most cases were a slight indisposition, lasting not to exceed a week, a diarrhea in the terminal stages and the refusal of food for two or three days before death. Sudden death without noticeable symptoms was occasionally observed. More striking, although not characteristic of the disease, were the symptoms of a transverse myelitis; the birds with this disorder were prostrated and showed a twitching of the limbs, which were in a constant state of extension. A palpation of the sternum, in many cases, disclosed a bilateral tumor-like induration along the keel bone. A history of an occasional death in the flock was generally obtained.

#### ENZOOLOGY

As a rule, the disease occurred sporadically in birds less than 1 year of age. It was most prevalent during the months of November, December and January; seldom was a case observed during the other nine months of the year. Two enzootic outbreaks were observed that sug-

8. Burgess, A. M.: Chloroma, *J. M. Research* **27**:133, 1912.

9. Brannan, D.: Chloroma: The Recent Literature and a Case Report, *Bull. Johns Hopkins Hosp.* **38**:189, 1926.

10. Boots, R. H.: Chloroma: With Report of a Case, *J. Lab. & Clin. Med.* **2**:622, 1916-1917.

11. Rowe, O. W., and Hirschboeck, F. J.: A Case of Myeloid Chloroma, *Am. J. Dis. Child.* **24**:239 (Sept.) 1922.

12. Goodall, A., and Alexander, W. A.: Acute Myelocythemia and Chloroma, *Quart. J. Med.* **17**:113, 1923-1924.



gested a potential economic aspect of the disease. The flocks concerned in the two outbreaks were small, totaling about sixty birds each. There was a mortality of 20 per cent in the first and a mortality of 10 per cent in the second flock during the months of November and December. In neither case were data of mortality obtained for the month of January, as the first flock was sold in the early part of that month and the owner of the second flock lost interest in the situation after receiving the same diagnosis on four separate occasions. Autopsies were not conducted on all the birds that died in the two flocks, but, at irregular intervals during the months of November and December, the owners presented birds to the laboratory for postmortem examination. In all the necropsies, the gross and microscopic pictures were of the neoplasm under discussion, and since all suggestions of a second disease were absent, it was assumed that the losses in these cases were due to the leukochloroma.

Twenty flocks were represented in the thirty-seven cases studied. The original source of six of these flocks was a flock in which annual,

TABLE 1.—*The Annual Incidence of Leukochloroma*

Periods of Observation	Number of Cases	Number of Birds Examined Postmortem	Incidence, per Cent
1925.....	3	595	0.5
1926.....	5	848	0.6
1927.....	11	1,177	0.9
1928.....	17	1,318	1.3

sporadic outbreaks of the disease were known to occur. The ancestry of three other flocks was probably the same, although this was not definitely shown. The ancestry of the remaining eleven flocks was not determined.

Table 1 gives the incidence of the disease as it was observed from year to year. In the year ending in June, 1925, an incidence of 0.5 per cent was observed and, with each subsequent year, an increased incidence was observed, the highest point, 1.3 per cent, being reached in the year ending in June, 1928.

The neoplasm was conspicuously present in Barred Rocks, although not confined to this breed, two cases having been observed in White Leghorns and a third in a White Rock. The majority of the cases occurred in females, an incidence that was undoubtedly influenced by market conditions, since most of the males had been disposed of as broilers before reaching the age at which the tumor, if present, usually destroys its host.

#### MORBID ANATOMY

The carcasses were those of well nourished fowls, and the amount of subcutaneous and visceral fat was frequently excessive. Emaciation was not encountered.

**The Neoplastic Growth:** Regardless of its location, the tumor presented a characteristic appearance. It was devoid of pigment, having the chalky-white, bloodless look that distinguishes it from the other common tumors of the fowl. It was exceedingly friable, disintegrating readily on slight manipulation. Necrotic areas were seldom seen, in spite of the fact that the pallid appearance suggested a scanty supply of blood.

**Sternum:** The point of union between the xiphoid cartilage and the keel bone was constantly the location for the tumor's development. Sometimes an incision of the muscle of the breast was required before the new growth could be revealed, but in the majority of cases there was an easily recognizable swelling at this point. In the well advanced cases, the tumor was from 2 to 3 cm. in thickness, and on examination was found to be an outgrowth from a much rarefied bone. The characteristic growth was also found with remarkable regularity on the internal aspect of the body of the sternum.

**Ribs:** An irregular chain of nodules or a cylindroid growth was usually found along the borders of the ribs. The periosteum of the ribs, as well as that of the sternum and the spinal column, was frequently intact, but was separated from the

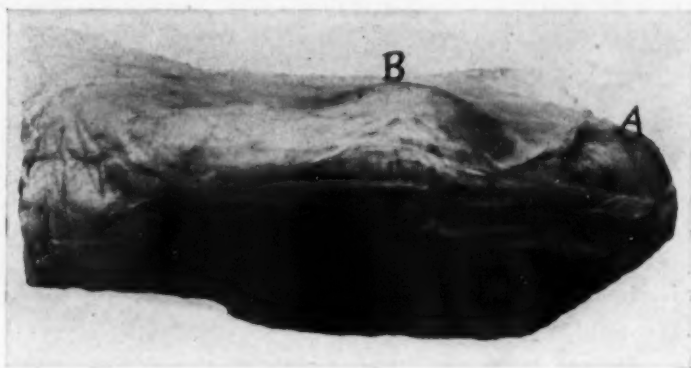


Fig. 1.—A primary leukochloroma involving the xiphoid cartilage, A, and a second and larger tumor located anterior to the first, B.

bone by the neoplastic growth. In many locations, the periosteum was infiltrated to such an extent that its gross identity was lost. Many of the bones, and especially the ribs, had a bleached appearance on account of the tumor's having replaced much of the red bone-marrow.

**Spinal Column:** In about 50 per cent of the cases, a neoplastic process involved the spinal column from about the middle of the thoracic region to as far back as the coccygeal vertebrae. The bodies of the vertebrae were sometimes dotted with the tumors, and sometimes their ventral surfaces were covered with a neoplastic mass that varied from 1 to 2 cm. in thickness. The bones were rarefied to a marked degree, and the new growth extended through the bodies of the vertebrae and into the spinal canal. The spine was easily fractured and offered but slight resistance when cut with a knife. The extension of the tumor into the spinal canal resulted in pressure on the spinal cord, a condition that explains most of the symptoms of transverse myelitis.

**Spleen:** The spleen, in some cases, was slightly enlarged, and in others it was increased to several times the normal volume. Occasionally, the organ had a

mottled appearance due to the formation of white, circumscribed tumors beneath the capsule; as a rule, however, the normal color was but slightly altered.

**Liver:** The liver, in about 65 per cent of the cases, showed gross evidence of metastases. The metastases varied all the way from a few circumscribed foci to

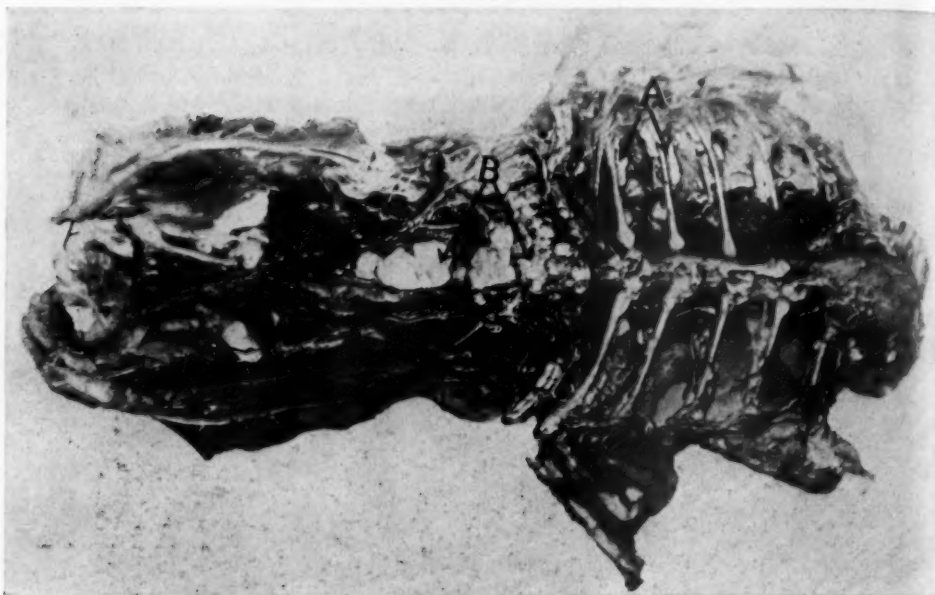


Fig. 2.—*A*, neoplastic nodules along the borders of the ribs; *B*, extensive ovarian involvement, and a large tumor posterior to the ovary.

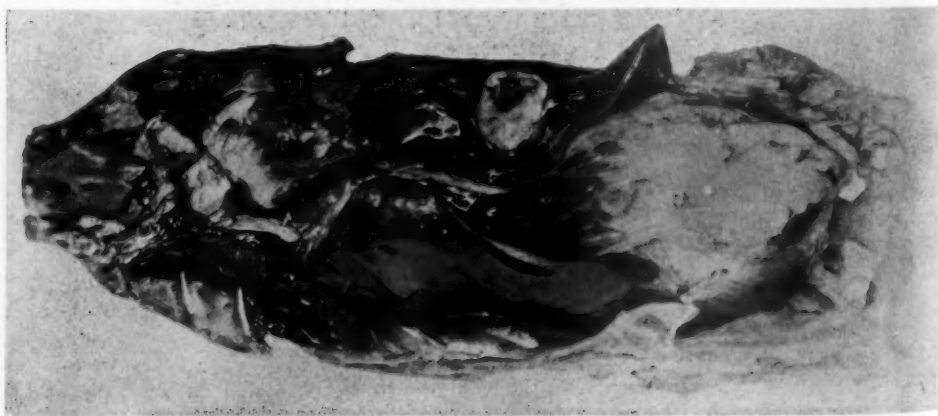


Fig. 3.—Metastatic leukochloroma, *A*, in the heart; *B*, in the liver.

a diffuse neoplastic growth that displaced most of the parenchymatous tissue. In the advanced cases, the liver was slightly enlarged, and it was not infrequently found ruptured.

**Ovary:** In the majority of cases, the ovary revealed an extensive neoplastic development. The organ was chalky-white and studded with an occasional atrophic graafian follicle.

**Kidneys:** Metastatic tumors were found in the kidneys with less frequency than in the liver or the ovary. When present, the white neoplasm stood out in bold relief against the maroon background of the parenchyma.

**Intestine and Pancreas:** The small intestine, especially the upper part of the duodenum, was frequently involved. In advanced cases, the walls of the intestines in numerous areas had been displaced by new growth. The marked intestinal

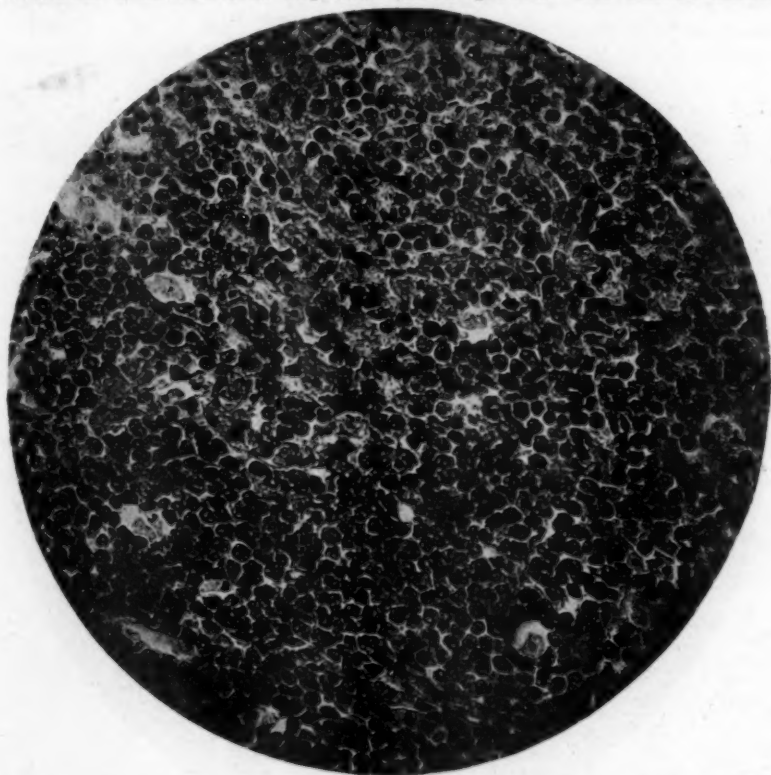


Fig. 4.—A section of the liver showing the parenchyma practically displaced by myelocytic cells.

involvement was generally associated with sharply circumscribed tumors of the pancreas.

**Heart:** In some cases, the epicardium was slightly elevated by new growths that extended into the myocardium to a variable depth. Similar growths occurred in the endocardium. The parietal pericardium was seldom involved.

**Lymph Glands:** The lymph glands were enlarged and in some instances showed nodular, neoplastic development.

**Other Organs:** Metastatic tumors were frequently found in the lungs. Unusual locations in which metastases occurred were the sciatic nerve, the esophagus, the gizzard, the trachea and the thyroid gland. The bones of the head showed a marked involvement in two cases.



## MICROSCOPIC CHANGES

**The Neoplastic Growth:** The tumor proper had an extremely cellular make-up. The cells were spherical, unless distorted by pressure, and were about equal in size to the mature avian myelocyte. Each cell had an eccentrically located, round or oval nucleus occupying about one half of the cellular space. Multinucleated cells were seldom found. The chromatin was disposed in the form of a fine reticulum, which appeared to radiate from a single nucleolus. Rapid growth was evidenced by an abundance of mitotic figures. In some cases, as many as twelve cells undergoing mitotic division were counted in a single field (4 mm. objective). The cyto-



Fig. 5.—Myelocytic cells infiltrating between the kidney tubules.

plasm had a definite outline, and was filled with numerous spindle-shaped granules, which took a brilliant eosin stain. The granules were of the same size and shape as those found in the mature myelocyte or the crystalloid polymorphonuclear leukocyte. The stroma consisted of a scanty reticulum, which gave the connective tissue reaction when stained by van Gieson's method. The supply of blood was more abundant than was suggested by the gross appearance.

**Liver:** On microscopic examination, the liver was found to be constantly the location for metastatic tumors. In the early cases, i. e., the cases in which gross evidence of an involvement of the liver was not observed, the neoplastic cells had a periportal distribution. In the well advanced cases, a diffuse infiltration and

filling of the sinusoidal spaces with myelocytic cells had resulted in the destruction of much of the normal parenchyma.

**Spleen:** The spleen presented the picture of a lymphoid exhaustion. In some cases, the splenic nodules were moderately engaged in the production of lymphocytes, but, as a rule, evidence was lacking that these structures had been recently engaged in the fulfilment of their normal function. There was a pronounced infiltration with myelocytic cells, which were found principally in the pulp and not in the splenic corpuscles. The infiltration of the pulp accounted for the splenic enlargement.

**Kidney:** One or both kidneys frequently showed numerous areas in which myelocytic cells had infiltrated the interstitial tissue. The epithelium of the



Fig. 6.—Metastatic leukochloroma in the kidney. The parenchyma shows moderate retrogressive changes.

tubules within the infiltrated areas showed considerable atrophy and fatty infiltrative degeneration, but not the pronounced necrosis that generally accompanies the infiltration of parenchymatous organs by some of the other types of malignant neoplasms. For the most part, pronounced necrotic changes did not accompany the infiltration of normal tissues by this type of tumor.

**Ovary:** The stroma showed a marked myelocytic infiltration. The graafian follicles were atrophic and few in number. The follicular epithelium was frequently pyknotic, and occasionally cells of myelocytic type were found floating in the liquor folliculi.

**Intestine:** The submucosa appeared to be the seat of metastases in the intestine. From this location, the infiltration progressed toward the lumen and the periphery until the epithelium was denuded and much of the muscular wall was displaced by the tumor.

**Heart:** Metastases in the heart occurred just beneath the epicardium and the endocardium. From these locations, finger-like processes infiltrated between the myocardial cells. The extent of the lesions suggested that metastases in the heart do not occur until late in the disease.

**Bone-Marrow:** Sections of bone taken from any part of the skeleton showed at least some neoplasm-like hyperplasia of the marrow. In many places, the normal constituents of the marrow were entirely replaced by mature myelocytes. The tumor, which in the gross appeared to be exuding from the bones, was found, in many cases, to be proliferating beneath the periosteum. In other cases, the periosteum was practically destroyed by neoplastic infiltration, but enough of

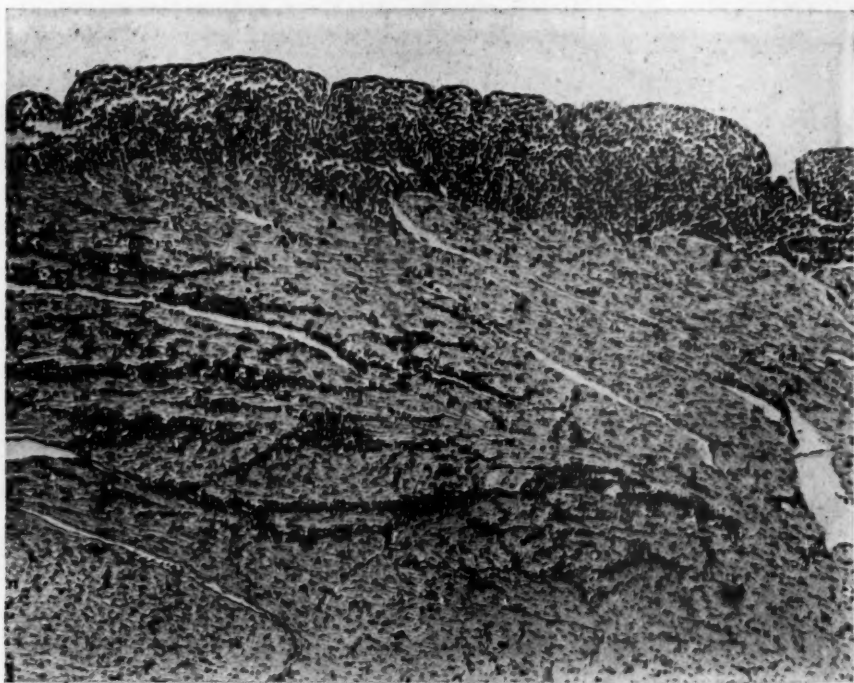


Fig. 7.—A section of myocardium showing a subepicardial tumor and an infiltration into the myocardium.

the normal tissue still existed to show that its normal relation to the bone had been lost. Cords of cells that connect the subperiosteal tumors with the neoplastic bone-marrow were easily demonstrated.

**Blood:** Fixed tissues prepared for microscopic examination, with one exception, showed the presence of numerous mature myelocytes in the blood vessels, and it was not uncommon to find cells of this type undergoing mitotic division within the blood stream. From these observations it was evident that a myelocythemia existed in most cases. Differential and total leukocyte counts were made on the blood of seven fowls, the results of which are given in table 2. A definite leukemia was found in all but one case (no. 220), and there was a high eosinophil count in this case. In preparing smears for differential counts, it was found that the eosinophil cells underwent a rapid degeneration, so that it was impossible to

differentiate between myelocytes and polymorphonuclear leukocytes. For this reason, all eosinophil cells were grouped under one heading. In six of the cases, there was a high eosinophil count; in the seventh, which is of special interest and will be discussed later, there was a marked lymphatic leukemia.

#### EXPERIMENTAL TRANSMISSION

Twenty-three fowls were inoculated with material from the tumors in three spontaneous cases.

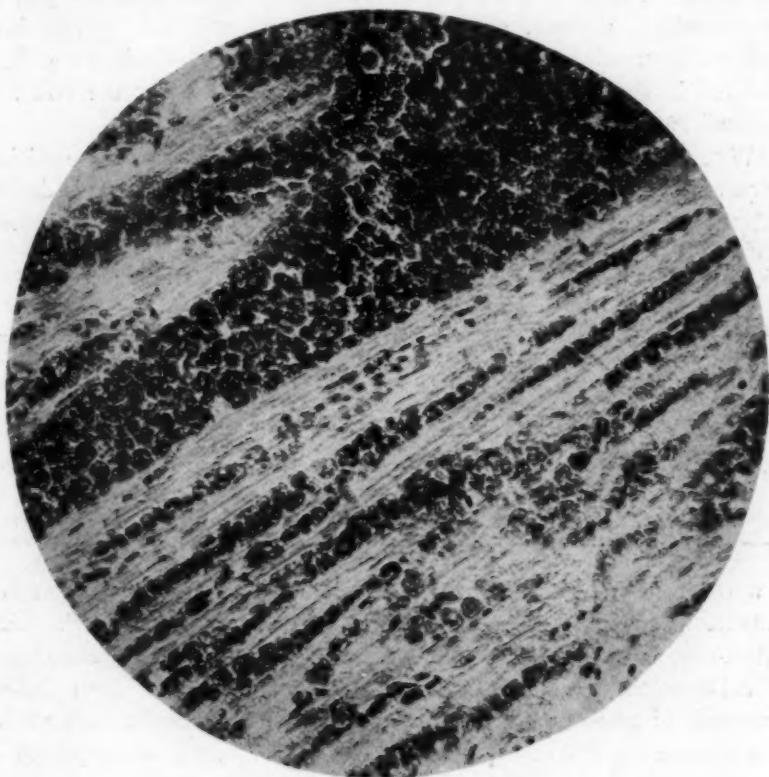


Fig. 8.—A higher magnification of figure 7.

The material was intraperitoneally transplanted into 12 and subcutaneously transplanted into 2. For 4, the inoculum was macerated in physiologic sodium chloride solution and injected intraperitoneally; the same inoculum was injected subperiosteally into 2. Large amounts of the inoculum were fed to 3 birds. The inoculations were completed within thirty minutes from the time that death occurred in the spontaneous cases. Five of the birds used for the experimental work were crosses of Barred Rock and Rhode Island Red; the remainder were White Leghorns. At the time of their inoculations the birds were from 2 to 12 weeks of age. At intervals ranging from three months to one year after the inoculations, the fowls were killed and autopsies made on them.



In not a case was there evidence, either gross or microscopic, that the disease was infectious and had been reproduced experimentally in these birds.

## COMMENT

A few conspicuous features of the chloroma of man are absent or of minor importance in the leukochloroma of the fowl. The green color has not been observed in the neoplasm in the fowl. However, this factor in chloroma can hardly be considered an essential part of the pathologic process, since both green and colorless tumors have been encountered in the same patient. Exophthalmia has not been observed in the disease in chickens. A predilection for the bones of the head has been noted in but two cases.

With the foregoing exceptions, the two tumors possess sufficient characteristics in common to warrant an assumption that one is dealing with the same disease in both species. Tumorous development resulting

TABLE 2.—*Total and Differential Leukocytic Counts in Seven Cases of Leukochloroma of Fowls*

Case	Total White Cells	Eosinophil Cells	Lymphocytes	Large Mononuclears
1.....	12,800	77	22	1
2.....	40,000	89	8	3
3.....	60,000	88	12	0
4.....	42,000	65	31	4
5.....	60,000	88	7	5
6.....	49,000	18	80	2
7.....	125,000	90	9	1

in a rarefaction of the sternum, the ribs and the spinal column is a characteristic manifestation of the disease in both man and fowl. Early metastases, especially to the liver, with no part of the body exempt, and an enlargement of the spleen and the lymph nodes without definite formation of a tumor are characteristics of the neoplasm in both species. The disease runs a rapid, fatal course, is frequently accompanied by neurologic symptoms and, as a rule, occurs during early life.

Histologically, the neoplasm in both species consists essentially of myeloid cells supported by a scanty reticulum of connective tissue and a supply of blood that is sufficiently adequate to prevent any pronounced necrosis. The important histologic changes in chloroma in man, which were shown by Dock and Warthin to consist of a tumor-like hyperplasia of the bone marrow, an enlargement of the marrow spaces, a rarefaction of the bone trabeculae and a direct extension of the neoplasm from the marrow spaces to the periosteum and surrounding structures, are found to be the essential pathologic changes in leukochloroma. Since the important histologic changes are found in the bones in both species, the disease should be considered a primary neo-



plastic overgrowth of the bone-marrow with direct extension to the periosteum and secondary metastases to other parts of the body. Widespread metastases that exhibit a rapid, diffuse infiltration into the normal structures are a constant part of the pathologic picture.

The leukemic stage of the disease in man is generally myelogenic in nature, at least to some extent. The presence of mature myelocytes in the blood vessels of fixed tissues indicates that the terminal stage of the disease in chickens is accompanied by a myelogenic leukemia.

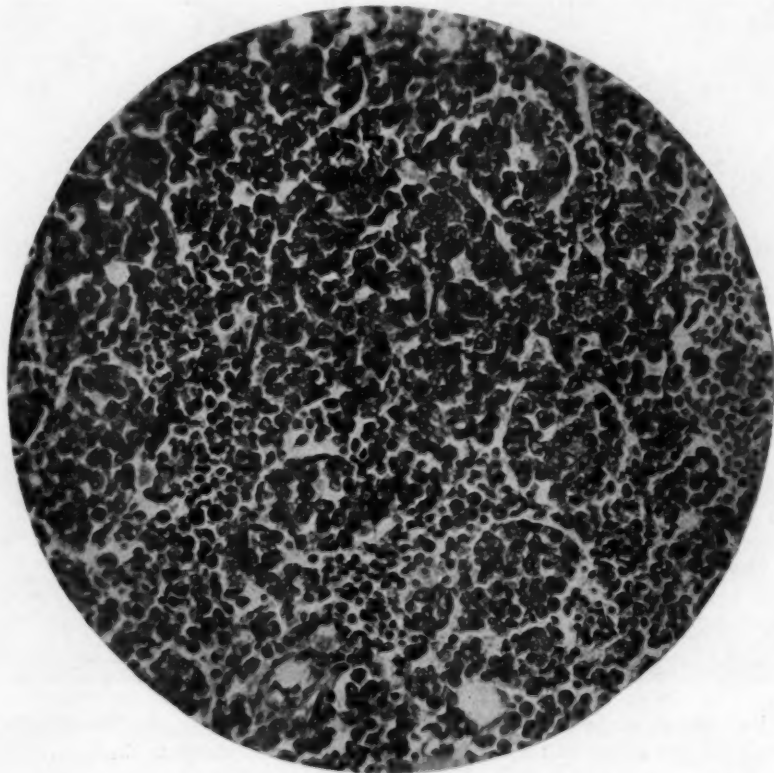


Fig. 9.—A section of bone-marrow showing the fat cells and other constituents of the marrow displaced by tumor cells.

Further evidence of a secondary leukemia is to be had in the differential leukocytic counts in six typical cases, in all of which there was a high percentage of eosinophil cells, and in five high white cell counts. Later, the examination of fixed tissues from these cases proved that the predominating white cells in the blood vessels were mature myelocytes. A secondary leukemia is therefore part of the syndrome in both species. An aleukemic stage of the disease in the fowl has not yet been demonstrated.

The experimental inoculations previously described were not of sufficient numbers to enable one to draw conclusions either for or against the infectious nature of the disease. They do not, however, support the observations of Ellerman and Bang,<sup>1</sup> Ellerman<sup>13</sup> and Schmeisser.<sup>2</sup> Ellerman and Bang observed myeloid responses following lymphoid inoculation and vice versa. From these results, they concluded that the two conditions were different manifestations of the same disease, and were caused by the same infectious agent. The frequency

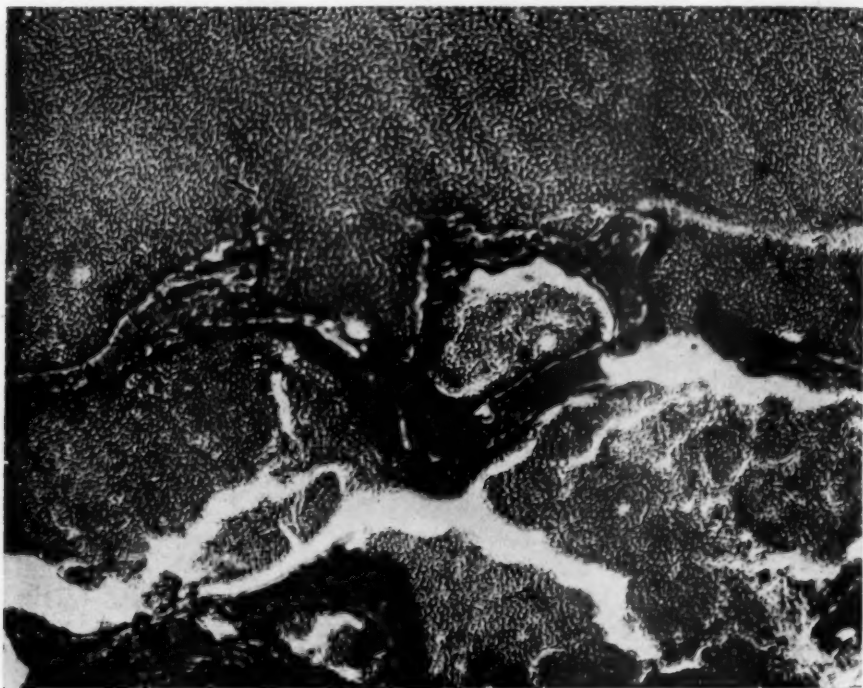


Fig. 10.—A section of bone showing enlarged marrow spaces. The neoplastic outgrowth has destroyed the normal relation of the periosteum to the bone.

with which lymphocytomas and leukochloromas are encountered in chickens and the fact that these two neoplasms are found much more frequently in some flocks than in others should prompt one to caution in interpreting experimental results of this nature. Research dealing with the etiology of the leukemias in fowls should be preceded by a thorough tracing of the ancestry of the birds to be used in the experimental work. Schmeisser frequently observed an icteric condition about

13. Ellerman, V.: A New Strain of Transmissible Leukemia in Fowls, *J. Exper. Med.* **33**:539, 1919.

the head, and a fibrinous pericarditis in his experimentally produced leukemias. These pathologic results are more suggestive of fowl typhoid than of either of the neoplastic leukemias. These observations, associated with the fact that he considered 80,000 leukocytes per cubic millimeter of blood to be within the normal limits for the fowl, lead one to suspect that more than one etiologic factor was operating in his experiments.

Winternitz and Schmeisser<sup>14</sup> noted myeloid infiltrations and proliferations in the liver, the spleen and the lymph glands of birds inoculated with material containing the organism of fowl typhoid, and from these and other pathologic results, concluded that they had produced "presumptive evidence" of a relationship between fowl typhoid and the neoplastic leukemias. Here, again, one finds it difficult to accept the evidence on account of the fact that myeloid changes, if present in the liver, are not a conspicuous part of the syndrome of fowl typhoid. We must therefore conclude at the present writing that the etiologic factor in the neoplastic leukemias of fowls has not been proved to be of an infectious nature.

Other investigators have considered the myeloid and the lymphoid neoplasms of fowls to be different manifestations of the same disease. This theory is not supported by my observations, although, during the past four years, I have made both gross and microscopic studies of 136 cases that were similar, in most respects, to the cases of lymphocytoma described by Warthin,<sup>15</sup> and by Tyzzer and Ordway.<sup>16</sup> The lymphocytoma presents, both grossly and microscopically, characteristics differing materially from those of leukochloroma. The former condition is commonly associated with emaciation and occurs in birds of all ages, whereas the latter usually occurs in well nourished birds less than 1 year of age. The lymphocytoma is gray. It is frequently associated with a profound enlargement of the liver. Although occurring in the bones, it does not produce the rarefaction and the neoplastic outgrowth into the periosteum and surrounding structures that characterize the leukochloroma. The bones in leukochloroma have a bleached appearance and are easily fractured, whereas, in lymphocytoma, the skeleton retains its normal rigidity. The leukochloroma has a characteristic chalky-white appearance. It is not associated with a profound enlargement of the liver. Not infrequently, one finds either the liver or the ovary showing a well advanced lymphocytoma with the other organs

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14. Winternitz, M. E., and Schmeisser, H. C.: Studies on the Relation of Fowl Typhoid to Leukemia of the Fowl, *Johns Hopkins Hosp. Rep.* **18**:25, 1919.

15. Warthin, A. S.: Leukemia of the Common Fowl, *J. Infect. Dis.* **4**:369, 1907.

16. Tyzzer, E. E., and Ordway, T.: Tumors in the Common Fowl, *J. M. Research* **21**:459, 1909.

not involved, so far as can be determined. Metastasis to other organs of the body is invariably preceded by an involvement of the bone marrow in leukochloroma.

Microscopically, the lymphocytoma is composed of cells resembling either the large or the small lymphocytes; the large myeloid cells are not encountered. The leukochloroma is characterized by large eosinophil myelocytes which do not in any way resemble the lymphocyte. Both diseases are associated with leukemia, but in the former the leukemia is lymphatic and in the latter it is myelogenic.

From the foregoing observations, it is evident that the two diseases are much more readily differentiated on a pathologic basis than are some of the more common diseases that are known to be of infectious origin. By reason of this, it appears to me that the lymphocytoma and the leukochloroma should be considered as two disease entities.

In view of the frequent occurrence of the two diseases, it is not surprising that both should be encountered in one and the same subject, especially if the diseases are later proved to be of an infectious nature. There was one fowl in the present series (previously mentioned) that showed a pronounced lymphatic leukemia. On autopsy, this fowl presented all the characteristic features of a lymphocytoma, and the presence of leukochloroma was not detected until a microscopic examination was conducted. In this case, the liver was found containing both lymphocytomas and leukochloromas. In some fields, the two types of cells were mixed; in other fields, the neoplasms were either purely lymphocytic or purely myelocytic. In addition to those in the liver, metastatic tumors were found in the gizzard, the ovary, the lungs and the kidneys. With the exception of the tumors in the liver, every one of the secondary neoplasms was entirely lymphocytic, and, in view of the evidence presented, this case was diagnosed as an advanced lymphocytoma with an early developing leukochloroma.

As previously stated, the disease is much more prevalent during November, December and January than at any other time of the year, and occurs, for the most part, in birds less than 1 year of age. It will be noticed that the seasonal occurrence follows by approximately from eight to eleven months, the three months of greatest activity on the part of the commercial hatcheries. Evidently, the age of greatest susceptibility accounts for its seasonal occurrence.

The fact that 30 per cent of the flocks concerned in the present investigation were found to have a common ancestry suggests that a hereditary factor is associated with the occurrence of the disease. The common ancestry in this case was a breed of Barred Rocks which is maintained on the same premises with other breeds of chickens, and although the disease makes an annual appearance, it is confined exclusively to the one breed. The occurrence of lymphocytoma has



also been found unusually prevalent in certain strains of fowls. Such evidence of heredity, although far from conclusive, is in keeping with the observations of Slye,<sup>17</sup> who stated that the occurrence of leukemia, pseudoleukemia, lymphosarcoma and kindred diseases has "followed the laws of heredity as surely as have neoplastic diseases." In other words, susceptibility to the neoplastic leukemias is regarded by her as an inherited mendelian recessive characteristic. It is this possibility of a hereditary factor which necessitates a thorough knowledge of the ancestry of the birds to be used, before experimental work on the neoplastic leukemias of the fowl is undertaken.

#### CONCLUSIONS

The common fowl is subject to a myeloid neoplasm that is associated with myelogenous leukemia. As a rule, the disease occurs sporadically in birds less than 1 year of age, but it may become enzootic. Analogies to the chloroma of man suggest the name leukochloroma.

The disease is analogous to chloroma in that it is a primary neoplastic hyperplasia of the bone-marrow with direct extension to the periosteum. The sternum, ribs and spinal column are common locations for the primary development. Metastases to all parts of the body are of frequent occurrence. The neoplasm is composed of myelocytes supported by a scanty connective tissue reticulum. There is a secondary myelogenous leukemia. The disease is most prevalent in the young. It runs a rapid, fatal course.

The etiologic factor in the disease has not been proved to be of an infectious nature.

The leukochloroma differs from the lymphocytoma of fowls in that the former is a disease of young birds. The bone-marrow is the seat of the primary development, which results in a rarefaction of the bones. The neoplasm is chalky-white. It is made up of mature myelocytes. The disease is associated with myelogenous leukemia. The lymphocytoma occurs in birds of all ages. It is gray. It does not produce a rarefaction of the bones. The neoplasm is composed of lymphocytes and is associated with lymphatic leukemia. On account of these features differentiating the two neoplasms, they should be considered as different disease entities.

There is evidence of an hereditary susceptibility to the neoplastic leukemias in mice. The evidence suggests that heredity is associated with the occurrence of leukochloroma.

17. Slye, Maude: Cancer and Heredity, *Ann. Int. Med.* 1:951, 1928.



# THE ARTERIAL SUPPLY OF THE KIDNEY IN NEPHRITIS

ITS RELATION TO THE CLINICAL PICTURE \*

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In the primary contracted kidney, progressive sclerotic thickening of the walls of the arterioles and narrowing of the lumen are considered adequate to explain the fibrosis and the shrinkage of the organ. Between the scattered areas of ischemic sclerosis and atrophy lie other areas of normal parenchyma, which may continue to meet the demands of urinary excretion until the kidney has contracted to an exceedingly small size. Before this reduction in size of the organ reaches a point incompatible with life, the prolonged strain of maintaining an arterial hypertension and the vascular changes in the myocardium often result in cardiac decompensation. It is therefore often not alone the reduction in normal secreting parenchyma but the additional burden of circulatory embarrassment that precipitates the renal insufficiency.

In still other instances, the end stages of the primary vascular disease are accelerated by the rapid development of necrosis and of inflammatory lesions in the walls of arterioles and small arteries throughout the kidney—the so-called malignant sclerosis of Fahr<sup>1</sup> or malignant hypertension of Volhard. This soon determines the onset of renal insufficiency and azotemia.

In chronic diffuse nephritis (the secondary contracted kidney), a primary glomerular damage initiates the pathologic process, although the tubules and the interstitial tissue are also always more or less involved. The subsequent sclerosis and contraction of the organ is generally ascribed to this diffuse disease. Although attention has been called by Loehlein,<sup>2</sup> Volhard,<sup>3</sup> Fahr,<sup>4</sup> Branch and Linder<sup>5</sup> and, most

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\* From the Mount Sinai Hospital.

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1. Fahr: Ueber Nephrosclerose, Virchows Arch. f. path. Anat. **226**:119, 1919. Henke and Lubarsch: Handbuch der speziellen pathologischen Anatomie und Histologie **6**:405, 1927.

2. Loehlein: Ueber die enzuendlichen Veraenderungen der Glomeruli, Leipzig, S. Hirzel, 1906.

recently, Fishberg<sup>6</sup> to the sclerosis of arterioles and small arteries in chronic diffuse nephritis, few clinicians have appreciated how characteristic and widespread are secondary arteriolar lesions in this disease.

Fishberg pointed out that the lesions of the vessels are essentially an endarteritis obliterans. He therefore believed that the obstruction to the peripheral blood flow in the damaged glomeruli is the causative factor. This would explain why the lesions are confined to the kidney in this disease and are, for the most part, absent in other organs. We fully agree with this explanation of the mechanism, but one must not forget that the changes in the arterioles are not unlike those that occur in any chronically inflamed tissue. Some of the changes in the vessels may be of this nature.

From morphologic studies of chronic diffuse nephritis, we have gained the impression that the vascular changes that occur in the advanced stages of this condition are often as extensive as in primary vascular disease and therefore cannot help but play a similar important rôle in the fibrosis and contraction of the kidney. If this conception is true, it may help to explain why the clinical pictures in the advanced stages of both arteriolar nephrosclerosis (primary contracted kidney) and chronic diffuse nephritis (secondary contracted kidney) often cannot be differentiated.

The kidneys in chronic diffuse nephritis differ in one important essential from those in primary arteriolar sclerosis. The former, unlike the latter, have, between the areas of ischemic sclerosis and atrophy, anatomically altered and functionally inferior parenchyma. As a result, they are rarely able to reach the extreme reduction in size of the kidneys in primary arteriolar sclerosis before azotemia and death terminate the process.

Until recently, these observations and conclusions were based only on impressions gained from microscopic studies. In order that the vascular disease in the secondary contracted kidney might be visualized more accurately, a method of injections to render the arterial circulation visible in all its ramifications was employed, which had been devised by Gross.<sup>7</sup>

3. Volhard, in Mohr and Staehelin: *Handbuch der inneren Medizin*, Berlin, Julius Springer, 1918, vol. 3, p. 1519.

4. Fahr (footnote 1, second reference, p. 1405).

5. Branch and Linder: The Association of Generalized Arteriolar Sclerosis with High Blood Pressure and Cardiac Hypertrophy in Chronic Nephritis, *J. Clin. Investigation* **3**:299, 1926.

6. Fishberg, A. M.: The Arteriolar Lesions of Glomerulonephritis, *Arch. Int. Med.* **40**:80 (July) 1927.

7. Gross: Studies on the Circulation of the Kidney, *J. M. Research* **36**:327, 1917; *ibid.* **38**:379, 1918-1919.

Bright<sup>8</sup> himself was the first to attempt a study of the circulation of the kidney in the disease that he described. The original publication contains his drawing of a kidney into which he had injected a colored solution. In response to a suggestion of Bence-Jones, Dickenson,<sup>9</sup> in 1860, perfused contracted kidneys and concluded that the increased resistance of the diseased organ to perfusion was not due to any change in the caliber of the renal artery or vein but to alterations in the more minute anatomy of the organ. In 1877, Thoma<sup>10</sup> came to similar conclusions. In 1925, Rigo,<sup>11</sup> repeating the experiments of Dickenson and Thoma, observed the same increased resistance to perfusion in both primary and secondary contracted kidneys. Within the past year, Doenecke and Rothschild<sup>12</sup> reported an increased resistance to perfusion in all types of contracted kidney associated with arterial hypertension, but failed to find any variation from the normal on perfusing the kidney in a case of subacute glomerulonephritis.

In 1916, Ghoreyeb,<sup>13</sup> using Wood's metal, made casts of the arterial bed of normal and diseased kidneys. The following year, Gross devised a more accurate method of injection, using a suspension of barium sulphate and gelatin in order to reach the glomeruli. Following the injection of this suspension, the organs were fixed, dehydrated and cleared and were also studied by means of stereoscopic roentgenograms. The architecture of the entire arterial tree, down to its minutest ramifications, was thereby visualized, both in normal organs and in contracted kidneys.

In normal organs, Gross observed a treelike arrangement with innumerable fine branches, the interlobular vessels, running a straight course perpendicular to the capsule and forming a broad even cortex. The normal architecture was that of a "spreading chestnut tree." As characteristic of the contracted kidney, he described, among other things, the marked diminution in the vasculature, the arterial tree being "withered and bare."

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8. Bright: Reports of Medical Cases, London, Longmans, Green & Company, 1827, vol. 1.

9. Dickenson: On Diseases of the Kidney Accompanied by Albuminuria, Med.-Chir. Tr. **43**:225, 1860.

10. Thoma: Zur Kenntniss der Circulationstoerung in der Nieren bei chronischer interstitieller Nephritis, Virchows Arch. f. path. Anat. **71**:42, 1877.

11. Rigo: Untersuchungen ueber der postmortale Durchstroemungskapazitaet des Nierenblutgefasssystems, Frankfurt. Ztschr. f. Path. **31**:1, 1925.

12. Doenecke and Rothschild: Ueber das Verhalten der postmortalen Durchstroemungskapazitaet der Blutgefasssystems der Niere bei Erkrankungen mit und ohne Blutdrucksteigerung, Zentralbl. f. inn. Med. **48**:866, 1927.

13. Ghoreyeb: Studies on the Circulation: 1. The Effect of Disease on the Renal Arterial Bed, J. M. Research **35**:87, 1916-1917.

Graham<sup>14</sup> recently employed a suspension of bismuth oxychloride in 10 per cent acacia and confirmed the changes that Gross described as occurring in the architecture of the arterial bed in the kidney in primary vascular disease. Graham's injection fluid was of such a consistency that it penetrated the glomeruli and also made it impossible to split the kidney before making the roentgenogram. The picture was therefore so dense that finer details were obscured. He injected the fluid into only one kidney in chronic diffuse nephritis and failed to find

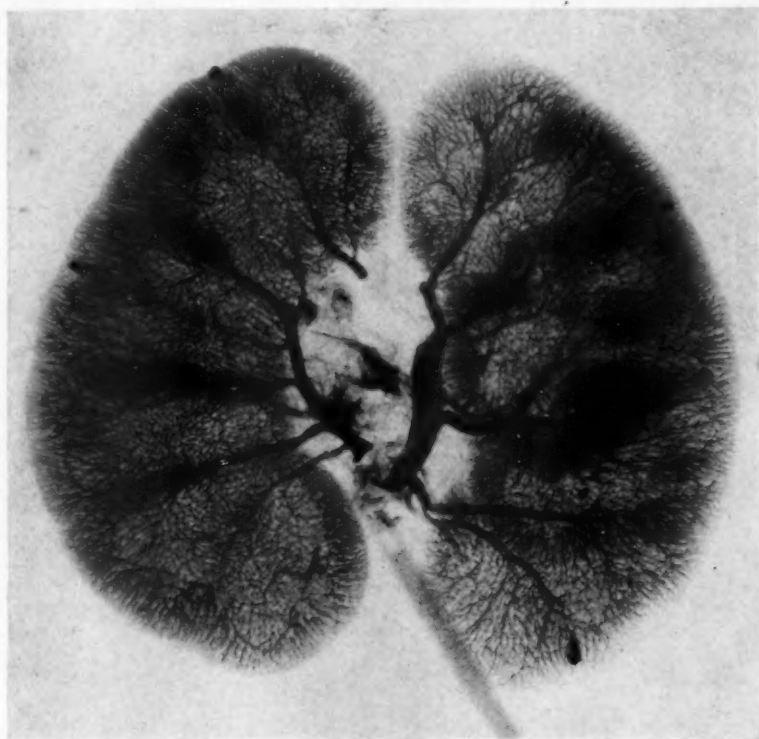


Fig. 1.—Normal kidney into which has been injected a mixture of barium sulphate and gelatin, according to the method of Gross. The numerous parallel arterioles in the cortex form a dense broad fringe.

any deviation from the normal vascular architecture. In view of the striking alterations that we have regularly observed in this disease, we are inclined to believe that the organ that he studied was not an advanced contracted kidney but was the seat of a subacute glomerulonephritis of relatively recent origin.

14. Graham: A Study of the Circulation in the Normal and the Pathologic Kidney, *Am. J. Path.* 4:17, 1928.

## EXPERIMENTAL OBSERVATIONS

Gross did not attempt to differentiate the various types of contracted kidneys into which he injected the suspension of barium sulphate and gelatin. It was therefore important to ascertain whether the remarkable diminution in vascularity in chronic "indurative" nephritis, described by him as giving the arterial tree a "withered and bare" appearance, was characteristic only of primary vascular disease of the kidney (primary contracted kidney) or whether it also occurred and reached the same degree of development in chronic diffuse nephritis.

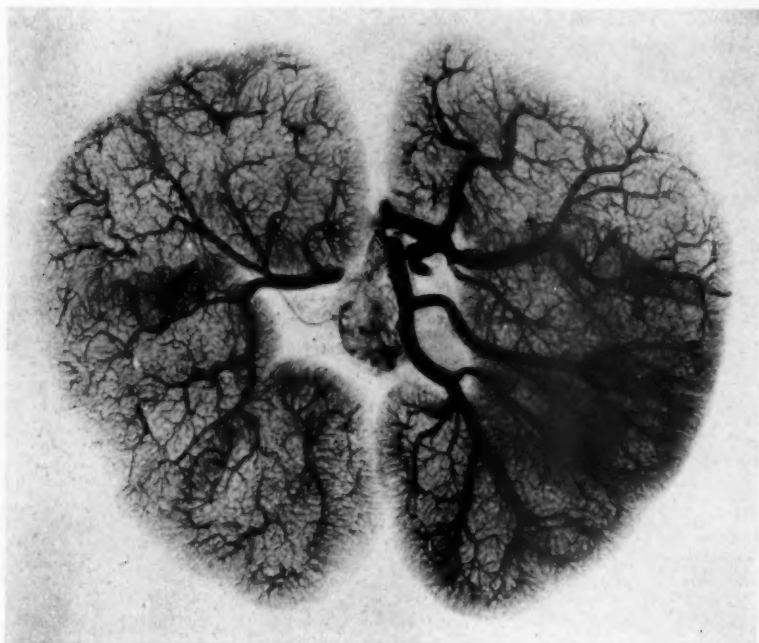


Fig. 2.—The kidney in arteriolar nephrosclerosis (early stage of primary contracted kidney). A marked reduction in the number of arterioles may be noted. The cortex is narrowed, and the arterioles in places run a more irregular and tortuous course.

*Primary Arteriolar Nephrosclerosis (Primary Contracted Kidney).*—Kidneys were obtained post mortem from three persons who had had uncomplicated cases of primary arteriolar nephrosclerosis. The barium sulphate and gelatin mixture was injected into the kidneys and the arterial tree studied in stereoscopic roentgenograms, and in the fixed specimens after they were cleared in methyl salicylate. A conspicuous diminution in the number of the finer branches of the arterial tree was observed, which approximated the withered and bare appearance described by Gross.

*Primary Arteriolar Nephrosclerosis Complicated by a Necrosing Arteritis and Arteriolitis (Malignant Sclerosis of Fahr).*—The kidneys from five persons who



had had typical cases of this disease, thus complicated, were studied following the injection of the mixture of barium sulphate and gelatin. The pathologic diagnosis was based on the criteria emphasized by Fahr.

Like the ordinary primary contracted kidney, these kidneys were much reduced in size, generally to half the normal size and weight. The surface was finely granular and the cortex markedly narrowed. On the other hand, the organs were extremely red, and both the surface and the cortex were conspicuously studded with hemorrhagic dots the size of a millet seed, decidedly larger than the hemorrhagic points seen in the so-called flea-bitten kidney of acute glomerulonephritis.

Microscopically, the differentiation was easily made. Throughout the organs, areas of parenchymal atrophy and fibrosis were seen, which had been caused by

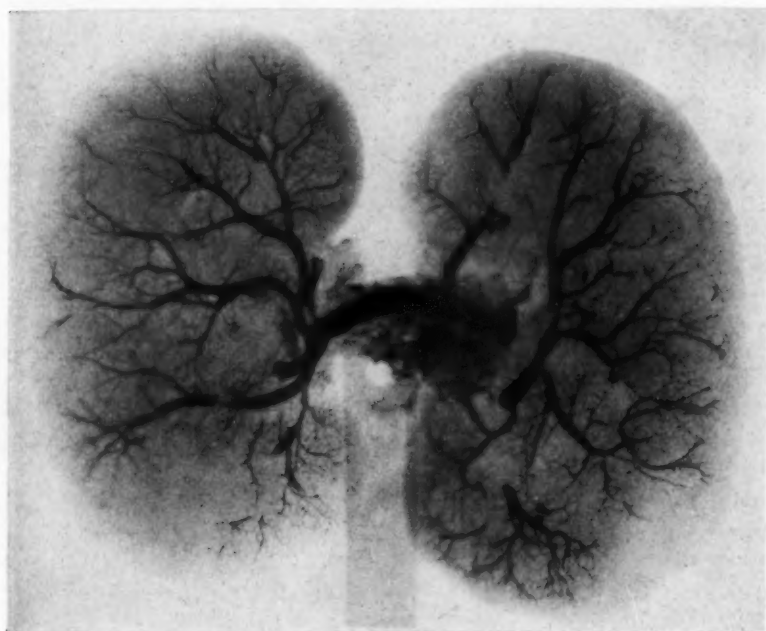


Fig. 3.—The kidney in arteriolar nephrosclerosis complicated by arteriolar necroses (malignant sclerosis of Fahr). Owing to closure of most of the arterioles in the cortex, the arterial system, on injection of a suspension of barium sulphate and gelatin, presents the appearance of a dead tree bereft of most of its finer branches.

arteriolar sclerosis. But, in addition, many arterioles and even arteries of medium size showed distinct necroses or inflammatory lesions of the walls. The intima in these sites was often greatly thickened, and the lining endothelium actively proliferating, so that the lumen of many of the small arteries and arterioles was being occluded. The necrotic lesions in the walls of the arteries and the proliferative changes in the lining endothelium and the intima were quite foreign to ordinary arteriolar sclerosis.

Also, numerous glomeruli supplied by these vessels showed necrotic lesions of many loops. Here and there, a necrotic loop had ruptured, resulting in a hemor-

rhage that filled Bowman's capsules and sometimes broke through and infiltrated the surrounding interstitial tissue. The capsular hemorrhages were generally larger than in ordinary glomerulonephritis, perhaps because of the high blood pressure in this condition.

Aside from the fact that the glomerular hemorrhages were more extensive than in ordinary glomerulonephritis, there were other alterations in the glomeruli that served to differentiate it from this condition: 1. Many glomeruli were not involved in the process; they appeared to be normal and their capillaries were filled with blood. 2. Many of the affected glomerular loops were not bloodless, as in acute

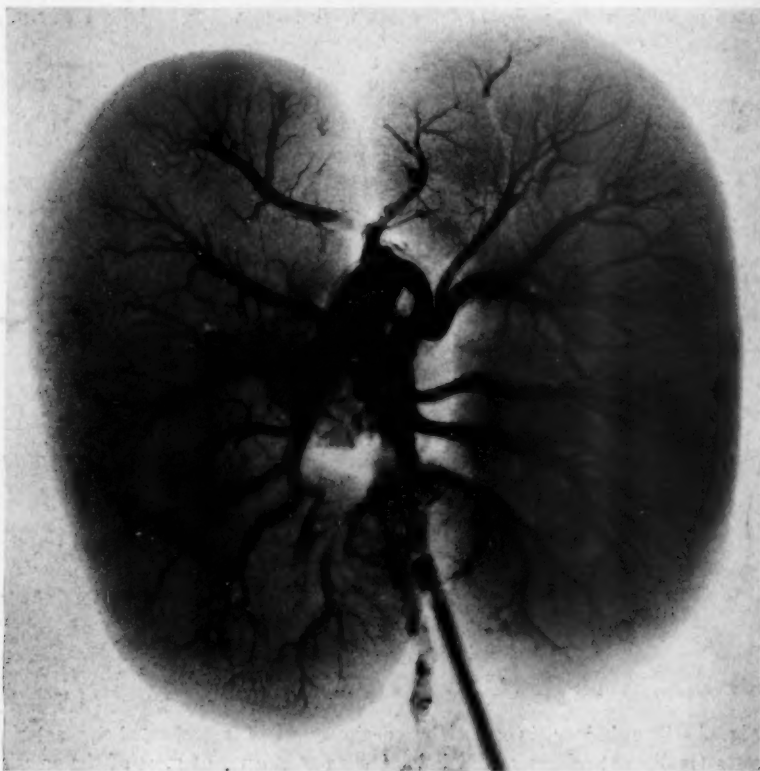


Fig. 4.—Kidney from another case showing the "dead tree" vasculature which is due to closure of the arterioles of the cortex by arteriolar nephrosclerosis complicated by arteriolar necroses (malignant sclerosis of Fahr).

glomerulonephritis. In fact, some of the damaged loops were full of blood. 3. The necrotic glomerular loops showed a peculiar hyaline droplet degeneration, which is not ordinarily seen in glomerulonephritis. Similar collections of hyaline droplets were also seen in the necrosing lesions of arterioles and arteries. 4. Although the endothelium of Bowman's capsule over the damaged loops was often swollen and desquamated, it rapidly succumbed to the necrosis. There was little tendency to form the crescents of proliferating epithelium often seen in glomerulonephritis.

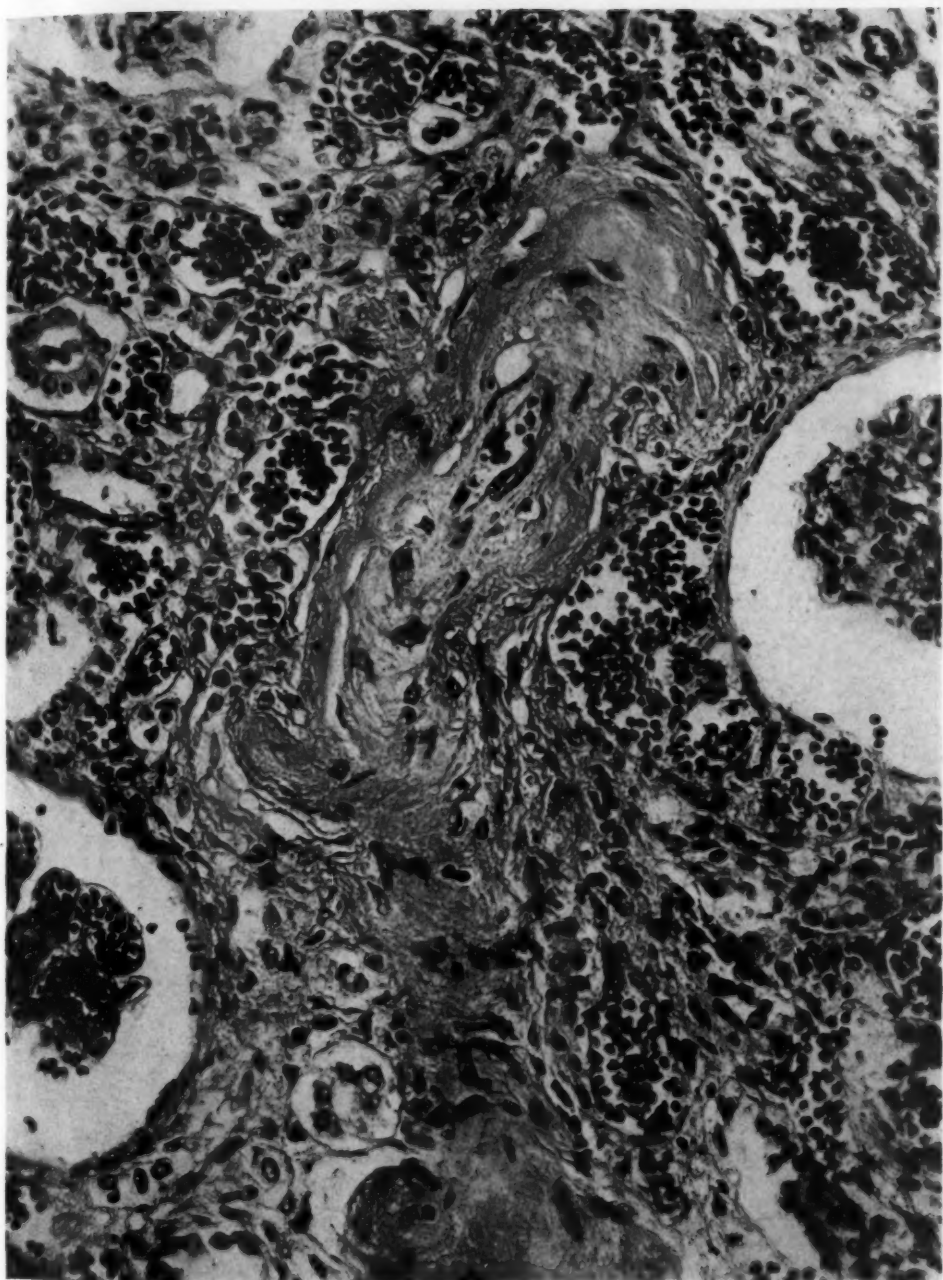


Fig. 5.—Arteriolar necrosis as seen in a microscopic section from the kidney shown in figure 3. Similar examples of a necrosing arteritis and arteriolitis occur throughout the organ. This photomicrograph illustrates the characteristic necrosis of the walls of the vessels and the rapid closing off of the lumen by a proliferative process in the intima.

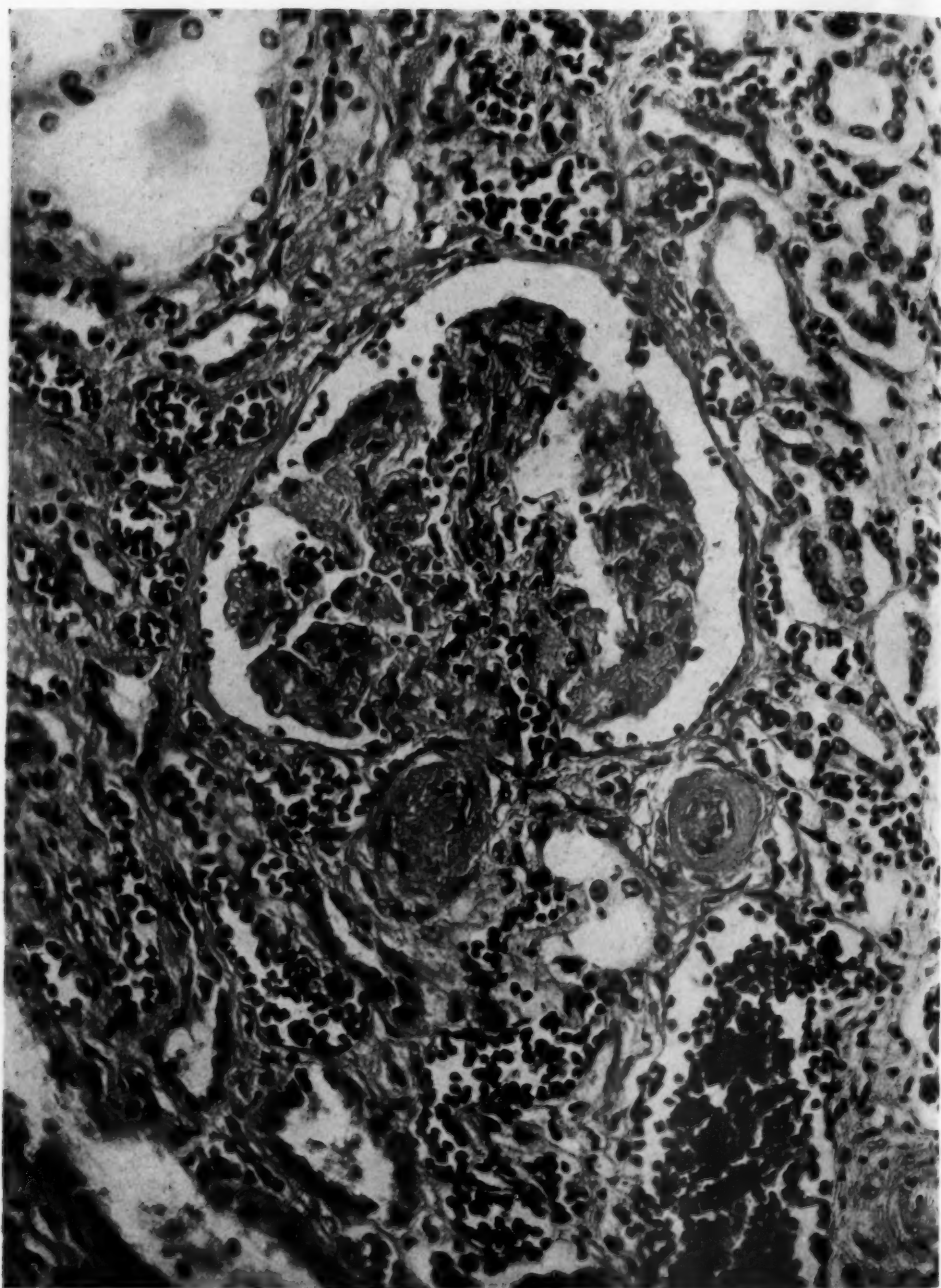


Fig. 6.—Arteriolar necrosis, with the characteristic necrosis of the walls of a vas afferens and the closing off of the lumen. The glomerular loops show a beginning necrosis and hyaline droplet degeneration. Some of the glomeruli in this kidney present a normal appearance, and many loops of affected glomeruli appear to be normal and contain blood.



The rapid closure of vessels resulted in atrophy or degeneration of areas of renal parenchyma and a tendency to round cell infiltration in the interstices.

There can be little doubt that these five cases constituted typical examples of the condition described by Fahr as malignant sclerosis. In kidneys that were already the seat of a slowly progressive arteriolar sclerosis associated with long standing arterial hypertension, there was superimposed a complicating necrosing arteritis with rapid closure of many of the smaller arteries and destruction of many glomeruli. Death occurred in dry uremia.

The kidneys into which the suspension of barium sulphate and gelatin had been injected showed an exaggeration of the changes described by Gross. The reduction

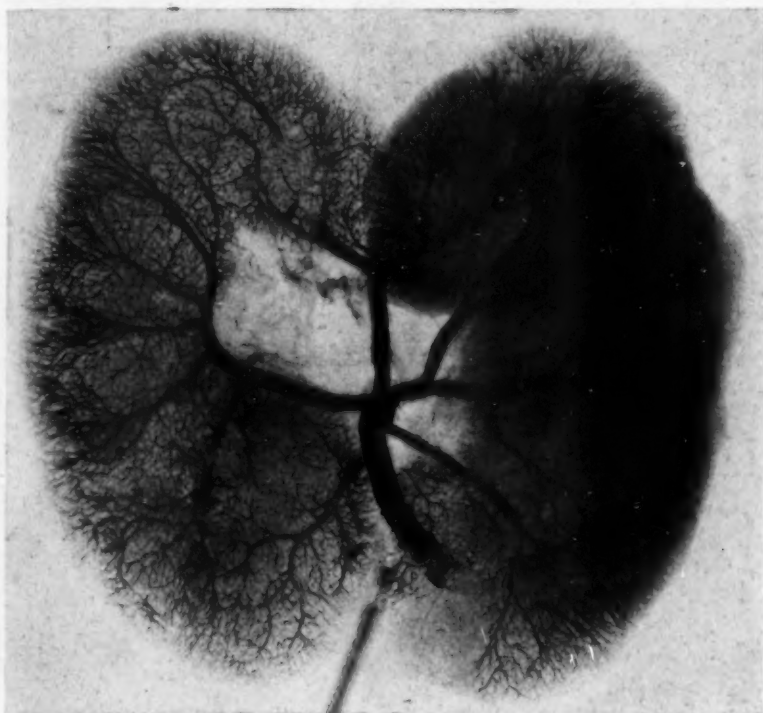


Fig. 7.—The kidney in subacute glomerulonephritis. Although the organ is swollen and edematous, there is not yet any conspicuous alteration in vascularity.

in the vascularity and the barren appearance of the vascular tree were marked. In fact, the vascular architecture in two cases was more like that of a dead tree, bare of most of its smaller branches.

*Acute and Subacute Glomerulonephritis.*—The kidneys in four cases of early diffuse glomerulonephritis were studied. Two of the patients had died in the acute stage of the disease within a month after the onset. They showed grossly the flea-bitten type of kidney. The kidneys from both patients presented, microscopically, a most severe diffuse glomerular disease. In one of these patients, complete anuresis had been present during the last fifteen days of life.

The other two patients had died approximately four and seven months, respectively, after the acute onset. The terminal clinical pictures had been characterized



essentially by the presence of nephritic edema, azotemia and arterial hypertension. The kidneys were distinctly swollen, the parenchyma gray brown and cloudy, and in one the surface still showed minute red points of occasional hemorrhagic glomeruli. Otherwise, the gross picture was that of the large white kidney. Microscopically, the disease was diffuse, all the glomeruli being more or less involved. Many contained typical crescent formations in Bowman's capsule. The epithelium in many of the primary tubules showed marked cloudy swelling.

A study of the kidneys by the injection method in all four early cases failed to reveal any gross alterations in the arterial tree. In the stereoscopic roentgenograms

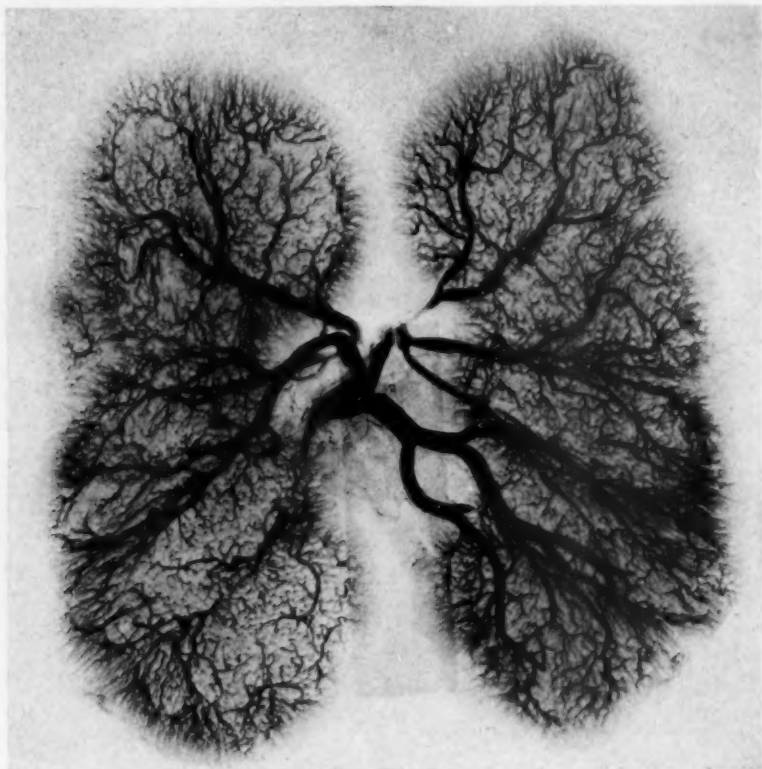


Fig. 8.—The kidney in chronic diffuse nephritis (secondary contracted kidney). A marked reduction in vascularity is shown. The cortex is narrow. The arterioles, which are much reduced in number, run a short and irregular course.

and in the cleared specimens, a reduction in the number of the finer interlobular arteries was not discernible. The arterial tree presented a complexity of architecture which could not be distinguished from that of the normal kidney. These early cases of glomerulonephritis served, therefore, as additional controls for the observations made in the later stages of this disease, the late secondary contracted kidney.

*Chronic Diffuse Nephritis (Secondary Contracted Kidney).*—Nine typical examples of secondary contracted kidney were studied by the injection method. Without attempting detailed description of the previous clinical course in each case.

it should be mentioned that in six of the series there had been a history either of a characteristic acute glomerulonephritis in early life or of a typical nephritic edema from which there had been apparently a recovery. In three of the cases, a history of a previous acute disease was not obtainable, nor had there ever been any symptoms suggestive of nephritis until the final illness. In all nine cases, the salient symptoms were those associated with the azotemia and the arterial hypertension. In only three of the cases was any terminal edema present, and in two of these it was insignificant. Essentially, the clinical picture of arterial hypertension and dry uremia could not be distinguished from that of the primary contracted kidney.

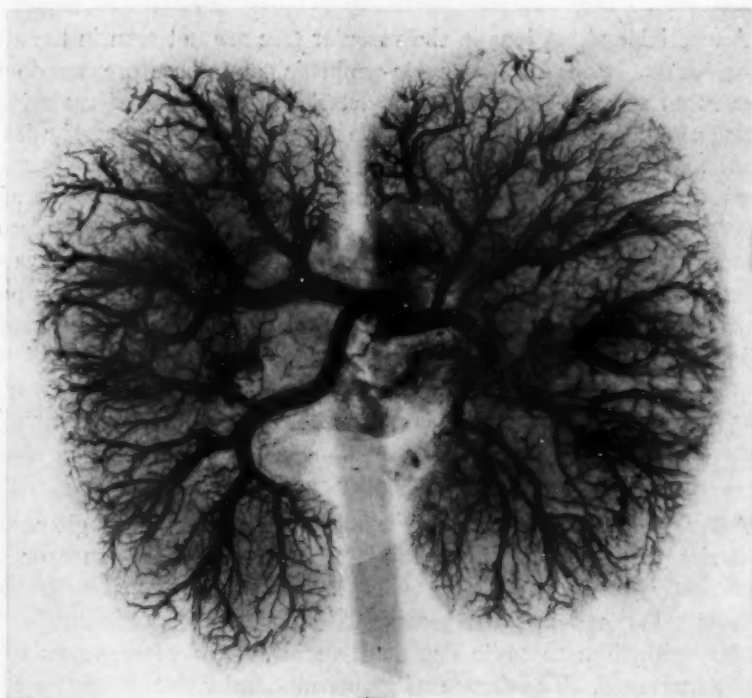


Fig. 9.—The kidney in chronic diffuse nephritis (secondary contracted kidney). As in figure 8, a coincidental reduction in vascularity and narrowing of the cortex are shown. In both instances, the original glomerulonephritis has long since run its course, and the pathologic process that is now responsible for arterial hypertension, renal insufficiency and death is identical with that of the primary contracted kidney.

The gross appearance of the kidneys was characteristic of secondary contraction—the moderate reduction to two thirds or one half the normal size and weight; the granular appearance of the surface, slightly coarser than that of the primary contracted kidney, and, in some, the occasional small islands of lighter colored parenchyma, which protruded on the surface and were evidences of a tendency to compensatory glandular hyperplasia or hypertrophy.

The chief microscopic criterion was the diffuse disease of the glomeruli, evidences of an old diffuse glomerular damage, as described by Loehlein.<sup>15</sup> In not a case did the microscopic observations permit room for doubt that a primary acute glomerulonephritis had initiated the pathologic process. The characteristic picture of diffuse disease of the parenchyma and sclerosis of arterioles resulting in areas of ischemic atrophy and fibrosis has already been described.

The arterial tree in all nine examples of advanced chronic diffuse nephritis, when the suspension of barium sulphate and gelatin had been injected, showed a most marked reduction in vasculature, approximately equal to that observed in advanced primary contracted kidneys. Without exception, the picture was that of the typical barren tree, and it was due to the obliteration of large numbers of arterioles and interlobular arteries.

Appreciable alterations in the vascular tree are not seen in the acute and subacute stages of glomerulo-nephritis, and therefore we do not believe that an acute damage to the arteries at the onset of the original disease can alone be responsible for the later changes. It cannot be denied that the diffuse glomerulotubular disease plays a part in the subsequent contraction of the kidney. But during the years that supervene after recovery from the diffuse nephritis, often several decades, a sclerosis of arterioles and a progressive and profound reduction in the vasculature of the kidney gradually take place, which eventually reach a point comparable to the condition of an advanced primary contracted kidney. As in the primary vascular disease, this similar reduction in vasculature due to the obliteration of many small vessels must produce atrophy of areas of renal parenchyma, replacement fibrosis and, finally, contraction of the organ.

#### CLINICAL-PATHOLOGIC CORRELATION

After recovery from acute glomerulonephritis, the glomerular capillaries that have not been completely destroyed are more or less permanently damaged; their walls remain thickened, hyaline and inelastic. Perhaps in part, because of this, the susceptibility of the tubular epithelium to toxic degenerative influences often seems to be greatly increased. The degree of glomerulotubular damage under these circulatory and toxic influences and its persistence probably determine the intensity of the albuminuria and, therefore, the occurrence of nephrotic edema.

Some cases of glomerulonephritis never pass through a nephrotic stage. Only a long latent symptomless period supervenes after recovery from the acute disease. During the latent period, which may last for several decades, the blood pressure may be normal and the urine may, at times, be entirely free of albumin.

Both types of cases, those that have and those that have not passed through a nephrotic stage, are represented in our series. In all, in the

15. Loehlein: Ueber Schrumpfnieren, Beitr. z. path. Anat. u. z. allg. Path. 63:570, 1916-1917.

course of time, arteriole disease developed, as widespread and as significant as in the primary contracted kidney. Concomitant with the appearance of these extensive sclerotic changes in the renal vascular bed, the blood pressure became conspicuously elevated. It is at present futile to speculate on the primary importance of arteriolar sclerosis in the causation of the arterial hypertension. Certainly the persistently high blood pressure may also conversely increase the tendency to arteriolar sclerosis and arteriosclerosis.

In this stage of chronic diffuse nephritis, the pathologic process is essentially identical with that of the primary contracted kidney—the gradual reduction in finer vasculature resulting in a progressive shrinkage of the kidneys. It is therefore not surprising that, if symptoms of the original diffuse nephritis have vanished, the clinical picture in both types of contracted kidney should be indistinguishable.

This fact has been the source of much confusion among clinicians. The clinical picture of arterial hypertension terminating in dry uremia is generally associated with the primary contracted kidney. It is indeed disturbing to the clinician to be told by the pathologist that the primary pathologic process was a glomerulonephritis and that the postmortem examination reveals an advanced stage of chronic diffuse nephritis. This apparent inconsistency is largely responsible for the statement heard from some clinicians that it is impossible to correlate the various clinical pictures of nephritis with the pathologic types observed at the post-mortem table. The observations that we have just reported remove one of the chief misconceptions in this regard. Pathologists have failed to visualize the pathologic process accurately. At this late contracted state of chronic diffuse nephritis, the primary glomerulotubular damage has spent itself, and the essential pathologic process, and hence the clinical picture, is now identical with that of primary vascular disease.

#### CONCLUSIONS

The reduction in renal vasculature in chronic "indurative" nephritis described by Gross is characteristic of both primary and secondary contracted kidneys.

In primary contracted kidney complicated by a necrosing arteritis and arteriolitis (the so-called malignant sclerosis of Fahr), the "barren and bare" appearance of the arterial tree is more pronounced, like a dead tree bereft of most of its finer branches.

Similar vascular alterations, as marked as those of primary arteriolar disease, develop in patients with chronic diffuse nephritis (secondary contracted kidney) who have survived the primary glomerulonephritis for a long enough period.

It has been universally believed that in chronic diffuse nephritis the diffuse parenchymal disease is alone responsible for the subsequent con-

traction of the organ. Our studies indicate that secondary arteriolar sclerosis plays a more important rôle in the production of the secondary contracted kidney.

The clinical picture of arterial hypertension terminating finally in dry uremia is generally considered characteristic of the advanced primary contracted kidney. In our experience, the secondary contracted kidney is much more commonly found at autopsy as the cause of this picture.

Studies based on arterial injection demonstrated that the terminal stages of the processes in both primary contracted kidney and secondary contracted kidney are pathogenetically identical: a progressive reduction in the finer vascularity of the organ resulting in a steady reduction in the amount of cortical tissue. It is, therefore, not surprising that these two types of renal disease, totally different at the time of their origin, should so often give rise, in their terminal stages, to identical clinical manifestations.



# THE EXCRETION OF METHYLENE BLUE (METHYLTHIONINE CHLORIDE, U.S.P.) BY THE BILIARY SYSTEM OF THE RABBIT

ITS SIGNIFICANCE FOR THE CONCEPTION OF HEPATOGENOUS STASIS IN THE GALLBLADDER \*

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There is considerable difference of opinion concerning the purpose and functions of the biliary vesicle. According to the most widely accepted view, the gallbladder is a reservoir with the function of supplying concentrated bile whenever there is call for such in the intestine. According to another view, of more recent conception, the bile enters the gallbladder not to be stored there and expelled in time, but to be resorbed in toto by the mucosa of the gallbladder. Thus it performs at least two main functions: first of returning important bile constituents into the circulation and second by the resorption of bile, relieving and regulating the pressure within the biliary system while the sphincter of the ductus choledochus is closed.

In other words, according to this hypothesis, bile which once has entered the gallbladder does not leave it again through the cystic duct under ordinary conditions, but is resorbed by the mucous membrane of the biliary vesicle, and the constituents then returned by the way of the veins and lymphatics into the liver and into the general circulation, respectively. The arguments for and against such a conception have recently been summarized by Kasper Blond.<sup>1</sup> The fact that bile may and does leave the gallbladder occasionally in small quantities does not invalidate the conception. Our experiments with methylene blue (methylthionine chloride, U.S.P.) on the rabbit<sup>2</sup> furnish substantial evidence, if not experimental proof, that at least in this animal, when bile leaves the gallbladder through the cystic duct, this is rather an exception than the rule.

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\* From the Department of Pathology and the Otho S. A. Sprague Memorial Institute, University of Chicago.

\* Read at the Chicago Pathological Society, Nov. 12, 1928.

1. Blond, Kasper: Eine neue Arbeitshypothese zur Klärung der Gallenwegsprobleme, Arch. f. klin. Chir. **149**:662, 1928.

2. Halpert, Béla; Rosi, A. L., and Hanke, Milton Theodore: Some Observations on the Function of the Gall-Bladder: Experiments with Methylene Blue on Rabbits, Anat. Record **38**:13, 1928.

It is not our purpose to present at this occasion all the data we have obtained on the excretion of methylene blue by the biliary system of the rabbit. We are more concerned at present with the data which illustrate the possibility of a hepatogenous stasis in the gallbladder, since this in turn, we believe, throws some light on the mechanism of the formation of biliary concretions.

Methylene blue injected intravenously or given by stomach tube appears in the bile, in which it can be determined by a quantitative method devised by one of us (M. T. H.). A brief description of this method and the results of some preliminary experiments with methylene blue on the rabbit have been published in the issue of the *Anatomical Record*<sup>2</sup> which contains the abstracts of papers presented at the meeting last April of the American Association of Anatomists.

In all of our experiments methylene blue was administered to rabbits in doses of 20 mg. per kilogram of body weight, that is, 2 cc. of a 1 per cent solution, in one series intravenously, in another by stomach tube.

It was found that methylene blue injected intravenously appeared in the bile in from three to fifteen minutes and reached a highest concentration—from 1:1,100 to 1:3,300—before the end of the second hour. Then, dropping gradually it showed from a fifth to a fifteenth of the highest concentration by the end of the sixth hour, the values ranging between 1:9,000 and 1:36,000. The bile removed from the gallbladder at the same time, i.e., six hours after the injection, usually contained from two to twenty-two times as much methylene blue as that contained in the last specimen of bile obtained from the ductus choledochus. Not only that, but at times the concentration of methylene blue in the bile removed from the gallbladder was much higher (1:720, 1:800) than the highest concentration ever reached in the bile collected from the ductus choledochus. The curve indicating the methylene blue content of the bile coming from the liver was a regular one: a sharp rise to the peak of a highest concentration was followed by a gradual decline. On the other hand, during the whole period of this decline and up to the end of the experiment, the methylene blue content of the bile in the gallbladder increased and at the end of the experiment was usually found to be many times higher than that coming from the liver. Had there been an occasional admixture of the bile from the gallbladder, with its high content of methylene blue to that coming from the liver, the curve of declining methylene blue concentration in the ductus choledochus would have exhibited irregularities. As the curve showing the methylene blue content of the bile collected from the cannulated ductus choledochus remained regular, however, it may be assumed that no bile left the gallbladder.

In the feeding experiments the amount of methylene blue given by stomach tube was exactly the same as in the experiments with injections.

Bile collected from the cannulated ductus choledochus twelve, eighteen, twenty-four, thirty and thirty-six hours after the administration of methylene blue by stomach tube contained little if any methylene blue. On the other hand, bile removed from the gallbladder at the same time invariably contained the dye. Bile collected from the cannulated ductus choledochus forty-two, forty-eight, sixty and seventy-two hours after the administration of methylene blue by stomach tube did not contain methylene blue. On the other hand, bile removed from the gallbladder contained the dye even after seventy-two hours in most instances.

When we examined the data on the feeding experiments more closely we noted that in none of the thirty-four animals which were opened between the twelfth and the thirty-sixth hours after feeding of the dye did the bile collected from the ductus choledochus contain methylene blue in a higher concentration than 1:23,000; as a matter of fact, in fourteen the bile did not contain any methylene blue. Yet the bile in the gallbladder of all of these animals contained the dye in concentrations between 1:1,200 and 1:10,000 in nineteen, and between 1:10,000 and 1:25,000 in eleven. The results in the forty-two, forty-eight, sixty and seventy-two hour groups of thirty-two animals are uniform. As mentioned before, in none of the animals did the bile collected from the cannulated ductus choledochus contain any methylene blue. Yet the bile in the gallbladder at this time contained the dye in more than half of the specimens, in concentrations ranging between 1:4,850 and 1:26,000.

In addition to all that has been said, attention should be called to the fact that the amount of bile delivered through the cannulated ductus choledochus during an experimental period of six hours averages about 10 cc. per hour; that is, the liver of a rabbit weighing 3 Kg. produces, conservatively estimated, 240 cc. of bile per day, and that the average capacity of the gallbladder of the rabbit is about 3 cc. Furthermore, in the feeding experiments the animals were kept on their usual diet, and there was always food in their cages. Under these conditions it is hard to conceive how methylene blue could remain in the gallbladder of an animal for a period of at least forty-two hours during which not less than 420 cc. of bile not containing the dye could have come from the liver, unless we give up the idea that the function of the gallbladder is to empty and to refill. The tenacity with which the dye is retained in the biliary vesicle long after the liver has ceased to produce bile containing the dye is surely one of the strongest arguments favoring the assumption that bile does not leave the gallbladder through the cystic duct under ordinary conditions. This circumstance, of course, calls for a change in the current conception of stasis in the gallbladder.

The term "functional biliary stasis" originated with John Berg, the Scandinavian surgeon. He urged<sup>3</sup> that a strict differentiation be made between the mechanical type of biliary stasis, i.e., one due to a mechanical obstruction to the free passage of bile into the duodenum, and a "functional biliary stasis" (mainly in the gallbladder) due rather to functional disturbances than to easily demonstrable anatomic conditions. "Functional biliary stasis," however, as conceived by John Berg, is a vague term, since its causes are unknown. Functional biliary stasis, as one of us has defined it elsewhere,<sup>4</sup> is a disharmony between the bile contained in the gallbladder and the resorptive function of the mucosa of the gallbladder. This definition of functional biliary stasis assumes, of course, that the mucous membrane of the normal gallbladder is capable of resorbing all of the bile constituents and that a disturbance of this resorptive function is the factor leading to stasis of bile in the gallbladder. The site of the process leading to stasis of bile in the biliary vesicle may be, of course, in the gallbladder itself, cystogenous stasis. Or, the quantity or quality of the bile produced by the liver may be such that the mucous membrane of the normal gallbladder is unable to resorb it completely, the liver rather than the gallbladder thus being responsible for the resultant stagnation. This type of stasis may appropriately be termed, as one of us has pointed out elsewhere, hepatogenous stasis. Finally, of course, both the gallbladder and the liver may be concerned.

Our experiments with methylene blue on the rabbit thus furnish a striking example of hepatogenous stasis in the gallbladder. With the bile from the liver a substance, methylene blue, is poured into the gallbladder; the mucosa of the latter apparently cannot resorb the dye fast enough to cause its rapid disappearance, and so the dye stays there for days.

This experimental result supports the idea that something analogous happens in cases of marked cholesterolemia, when the cholesterol content of the bile is correspondingly exaggerated. Apparently due to the increased output of cholesterol by the liver, the mucosa of the gallbladder becomes, so to speak, saturated with the lipid substances which it has resorbed from the bile. In such conditions, the cholesterol content of the bile in the gallbladder becomes greater and greater, and while the other bile constituents, those holding the cholesterol in solution, are being resorbed, the concentration finally may reach a point at which the cholesterol will crystallize out at the slightest provocation.

3. Berg, John: Einleitungsvortrag zum Thema "Gallensteinleiden," Arch. f. klin. Chir. **126**:329, 1923.

4. Halpert, Béla: Neue Wege in der Gallenblasenforschung, Med. Klin. **20**:408 and 1830, 1924.

In conclusion, we may say that the significance of the data obtained from the experiments with methylene blue on rabbits is manifold:

1. The data contribute experimental evidence that the bile does not, under ordinary conditions, leave the gallbladder through the cystic duct.
2. They furnish a striking example of stasis in the gallbladder for which the liver is responsible (hepatogenous stasis).
3. In view of the possibility of creating conditions analogous to those described here for methylene blue, but with agents with more pronounced bactericidal action, they may indicate the road leading to a much desired goal, a successful chemotherapy of the gallbladder.



## General Review

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### THE PATHOLOGY OF PRIMARY CARCINOMA OF THE LUNG \*

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Interest in carcinoma of the lung and bronchi is gaining momentum if one may judge by the rapidly growing literature on this subject. The nature of the disease is such as to compel the attention, and invite the contributions, of those concerned with several branches of medical science. The internist, the surgeon, the radiologist and the bronchoscopist each feels that it lies peculiarly within his field, while to the pathologist it presents certain as yet unsolved problems that prove exceedingly attractive. No other form of neoplastic disease is more intriguing from the standpoint of incidence than primary carcinoma of the lung, for within a generation it appears to have become one of the common forms of malignant disease, instead of the rarity which it was believed to be at the beginning of the present century. Is this alteration in incidence real or only apparent? If it is real, and many competent pathologists are convinced that it is, what are the factors in the life of the time which have brought about such a change that one now sometimes sees the word "epidemic" figuratively used in connection with this condition? Answers to these questions will be of importance, also, in connection with the problems of malignant disease in general.

Recent rapid advances in thoracic surgery challenge the internist and the clinical pathologist to diagnose carcinoma of the lung at a sufficiently early stage so that surgical intervention will be possible. This is rarely accomplished, although the diagnosis is being made more and more frequently on the living patient rather than at autopsy. The roentgenologist, aided by intrabronchial use of radio-opaque substances, and the bronchoscopist, supported by microscopic biopsy, are at present the chief aids in securing early diagnosis. Thus from many sides have arisen interests which have so augmented the literature of primary carcinoma of the lungs and bronchi that it is unusual to open a journal without finding some reference to this subject. Many interesting reports of cases of carcinoma of the lung are concealed under other titles. For instance, Yokohata's paper on microscopic metastases of cancer in the spleen contains descriptions of four typical cases of carcinoma of the lung. An annotated bibliography if complete would, alone, exceed the limits of this review.

## HISTORICAL NOTE

Of necessity, the early history of primary carcinoma of the lung lies in obscurity. The best historical survey is that of J. Wolff, who has reviewed rather critically some of the earlier references. Morgagni's description of a case in 1761 is sometimes quoted as the earliest gross account of primary carcinoma of the lung. It rests on slender evidence. A man, 36 years of age, who had had blood-streaked sputum, a cough and pain in the chest, died on the seventh day of the disease "in consequence of his expectoration being wholly suppressed." Bilateral pleural adhesions were found, particularly heavy over the upper right side anteriorly. Here a "cancerous ulcer lay hid in the lungs, the seat, perhaps, of an inveterate disease." A polypoid mass in the right ventricle provided a possible explanation of pulmonary infarction. A second observation made on a woman 40 years of age, who had a large tumor of the heel, certainly had to do with metastatic sarcoma of the lungs. A case observed by van Swieten, in which the upper portion of the right lung of a man 50 years old was scirrhus, may well have been pulmonary carcinoma, although esophageal carcinoma could not be definitely excluded.

The term "phthisie cancéreuse" was used by several writers before 1810, but their descriptions left uncertainty as to the primary neoplastic nature of the conditions described. In that year Bayle, under this same name, described three cases. The first was that of a man, 55 years old, who was attacked with dyspnea and a dry cough and had a mucopurulent sputum with hemoptysis. The duration of the disease was eighteen months. A soft, fluctuating tumor finally appeared above the right clavicle. At dissection, both lungs were found to contain numerous tumors of rounded form and of a lardlike consistency. Although other primary growths were not found in the body, the description of the tumors in the lung suggests that they may have been metastases. Bayle's second case, in which numerous encephaloid tumors were found in the lungs of a man 35 years of age, who had suffered amputation of the arm for a rapidly growing tumor, was certainly an example of pulmonary metastasis. The third case was that of a man, aged 72, whose illness was thought to be of but six weeks' duration. Pain in the chest and epigastrium, cough, white opaque sputum, obstipation, enlargement of the liver and three small hard movable bodies in the epigastrium and the right hypochondrium were the symptoms. At dissection, the root of the left lung was found to be occupied by a shining, white, medullary mass. In this and in the lung itself, tuberculous areas could be distinguished from those which were cancerous. The presence of numerous large metastases in the liver rendered doubtful the primary nature of this case which might have been a bronchiogenic carcinoma so far as the description of the lung itself is concerned.

William Stokes, in 1837, stated that cancerous disease of the lung was to be encountered in two forms. In the first, a degeneration of the lung occurred so that it was transformed into a cancerous mass without any tumor being produced. In the second, the scirrhus or encephaloid matter formed a tumor which was at first external to the lung, but ultimately displaced it. He recognized the great variety of physical manifestations which an intrathoracic mass of the second type could produce through displacement of the lung, compression of the esophagus, trachea or bronchi, or the obliteration of the subclavian or carotid arteries or of the innominate vein. Later, in 1842, he collected and analyzed a group of cases of malignant disease of the lung, partly from his own experience and partly from the literature, including the important case of Graves, which was the first in which a careful physical examination was carried out. In this paper, Stokes discriminated between nine different types of thoracic cancer and noted the combination of that condition with empyema, with pulmonary gangrene, with bronchiectasis and with bronchitis. Although obviously secondary carcinoma is confused with possibly primary cancer among the cases quoted, sound clinical observations were made and important principles were formulated. These may be illustrated by quoting from a long list of conclusions.

That dysphagia, tracheal stridor, feebleness of one pulse, difference of respiratory murmur from pressure on the bronchial tube, displacement of the diaphragm and dilatation of the heart may occur.

That the following symptoms are important as indicative of this disease: pain of a continued kind; a varicose state of the veins in the neck, thorax, and abdomen; oedema of one extremity; rapid formation of external tumors of a cancerous character; expectoration similar in appearance to currant jelly; resistance of symptoms to ordinary treatment.

These early observations were followed by a constantly increasing number of reports of cases. The development of histopathology led to analyses based on the types of cells that characterize the structure of the growths and to classification according to histogenesis. Thus, near the end of the century, the important studies of Kurt Wolf and of Pässler collected the available cases. Reinhard had found twenty-five cases in 1878 while Wolf listed thirty-one in 1895. Not all of these were microscopically verified. In 1891, Werner could find but nine fully verified cases, but in 1896 Pässler listed seventy which he believed to be authentic. Adler's monographic work published in 1911 was based on 374 cases of carcinoma of the lung and 80 cases of sarcoma, but here, again, some cases were admitted without microscopic verification and others in regard to the primary nature of which serious doubt must be entertained. 1.



In more recent years, the great apparent increase in the number of cases of primary carcinoma of the lung has stimulated statistical study and speculation as to the etiologic factors. The tumors of the lungs of the Schneeberg miners have been reconsidered. Much attention has been given to the possible effect of pandemic influenza as a cause of increased incidence. The past ten years have been characterized by a realization of the great frequency of primary carcinoma of the lung and of the importance of this localization in connection with the whole problem of cancer.

#### INCIDENCE

*Inherent Weakness of Most Statistical Studies.*—As is true of all cancer statistics, those dealing with primary carcinoma of the lungs and bronchi are of value only to the extent that the material units have been critically selected. The authenticity of the individual case is the crucial test. Obviously, only those reputed examples of primary carcinoma of the lung are of value on which a complete autopsy has been done. Certainly, too, there must be microscopic verification of each case, if results are to be fully accepted. Routine microscopic examination reveals many errors in the conclusions of even the most experienced gross pathologists. Doubtful cases should be excluded from collected series. For instance, a patient with massive infiltration of the mediastinum and root of a lung and a small hard nodule of the same type of carcinoma in the thyroid is more apt to have a primary carcinoma of the thyroid than a primary bronchiogenic carcinoma. Also, those examples in which multiple separate masses of carcinoma are found in both lungs and primary carcinoma is not observed elsewhere, are best interpreted as instances of hidden primaries. Every experienced prosector can recall autopsies in which painstaking search failed to disclose a primary site of malignant growth although abundant secondaries were present in the lungs or the liver. The microscope might have shown in such cadavers a small area of long standing malignancy in the prostate, breast, thyroid or elsewhere. Cases are encountered, too, in regard to which positive conclusions cannot be drawn even with thorough microscopic study. In the desire to have extensive series of cases to report these and other errors have been allowed to become both frequent and obvious in many of the collected series. In studies which are only statistical, the reader is at a loss to know how critical the compiler may have been in selecting his original units. There is still need for statistical studies based on carefully selected and fully authenticated cases of carcinoma of the lung.

*Spontaneous Occurrence in Animals.*—Primary neoplasms of the lungs and bronchi have been numerous reported as discovered in the lower animals, in a wide range of genera.<sup>11</sup> Many of these tumors were



not well studied, so that there is doubt as to the primary cancerous nature of some which have been so classified. Those interested in the wide occurrence of neoplasms of the lung in general will find much of interest in the compilations of Fox and Sticker. Fox found only 4 primary tumors of the lung among 34 neoplasms discovered in 2,533 wild animals dying in captivity on which he made autopsies. These occurred in the musky lorikeet, Malayan civet and rabbit-eared bandicoot. Sticker found 30 cases of primary cancer of the lung among 1,026 instances of primary cancer of all organs occurring in domestic animals. //

Fuchs, in 1886, described what he believed to be a primary bronchial carcinoma of the cat. Both lungs were involved in a nodular manner; the microscopic picture was that of a mucin-producing, cylindric-cell adenocarcinoma and there were metastases to the bronchial and axillary nodes. Diffusely infiltrating carcinoma of the lung of the cat was described also by Kitt, and Sticker found the lung to be the site of 3 of the 21 instances of primary carcinoma that he listed for this animal.

In the dog, Sticker found 10 malignant neoplasms of the lung in 766 autopsies. The earliest recognition of primary carcinoma of the lung in this animal appears to have been that of Johne (1880), although he did not give a detailed histologic description. A carcinoma made up of large cylindric cells in a lower lobe of a lung of a dog was reported by Seigert. Metastases were not found. A similar neoplasm was described by Liénaux, while the mucinous carcinoma of the lung reported by Rievel was thought to have had its origin from the flattened alveolar epithelium and to have undergone a secondary mucinous degeneration.

Few reports of primary carcinoma of the lung in cattle are to be found in the literature. Sticker was able to collect but three cases and these were of uncertain value.

Primary carcinoma of the lung in horses has been described several times (literature reviewed by J. Wolff). Grammlich's case showed a left bronchus broken through by the neoplasm.

Wolff was able to collect three probably primary epithelial neoplasms of the lungs of sheep. One of these, that of Eber, is of special interest because of the diagnosis of "*adenoma proliferum papillare*," suggesting that it might have been similar to the neoplasms which are common in mice. It was believed, however, to have had its origin in the mucous glands of the bronchial wall. Atypical, but nonmetastasizing, epithelial proliferations, which were chiefly of alveolar origin, occurred in the lungs of sheep suffering from the South African disease called "*jagziekte*" (Cowdry). These were often extensive and presented a definite adenomatous appearance. An annular bronchial polyadenoma of unknown causation was described in the sheep by Ball.

In the rabbit, as in the guinea-pig, carcinoma of the lung must be rare indeed, considering the large number of these animals which are examined in various laboratories in which the presence of a neoplasm would arouse interest. Wolff was able to collect but two examples for the rabbit. One of these was described as a "carcinoma simplex," the other as an "epithelioma." He listed a single "adenoma" as the only primary epithelial neoplasm of the lung of the guinea-pig reported up to the time of his study. Apparently the rat is also relatively free from spontaneous pulmonary carcinoma. In connection with the examination of rats for the plague at San Francisco, McCoy did not find one with tumor of the lung, although 103 with other tumors were discovered.

Primary epithelial tumors of the lungs of mice have attracted attention. The first of these was described by Livingood in 1896. A small white boss, about 5 mm. in diameter, was found projecting from the surface of the lung. Microscopically, this small mass was thought to present the appearance of an adenocarcinoma, and at one point it could be seen to arise from within a bronchus, growing as a papilloma within its lumen but breaking through the wall of the bronchus and dispersing in the surrounding tissue. Haalund evidently saw the same type of growth in 1905. Tyzzer described a number of such tumors in detail in the following two years. Among about 800 mice he found 16 with spontaneous primary neoplasms and 12 of these had what might be termed "papillary cystadenomas" of the lungs. In only one instance was the tumor large enough to interfere with function. An encysted worm was present in one lung, but it was not in relationship to the tumor. All of these tumors corresponded to a single type, but with minor variations. They were all situated at the periphery of the lung and were covered externally by pleura and consisted essentially of irregular folds and processes of supporting tissue covered by epithelium. Some were more cystic, and others more compressed, than the general type. These growths seemed to be primarily independent of the bronchi, but this point could not be definitely determined in each instance. While multiple nodules were found in some cases, proof of metastases was lacking. Nevertheless, the extension of the tumor into the bronchi, in two instances, was taken to indicate the malignant character of this type of growth. Haalund subsequently examined 30 nodules in the lungs of 19 mice. Most of these were small adenomatous nodules and did not exhibit signs of active growth. Some, however, invaded the surrounding lung tissue and the lumina of the bronchi and of the blood vessels. One nodule composed of squamous cells was found. The theory was advanced that the adenomatous nodules might have developed at the sites of earlier infarcts due to nematodes. This was based on the distribution of the lesions and could not be definitely proved, but was an attractive suggestion, for such verminous

infarcts were found in corresponding areas of the lung. Tyzzer added four or five examples of the epidermoid type, in a later report, which included also his earlier cases of the type of cystadenoma, making a total of 52 neoplasms of the lung in a series of 83 tumors. At about the same time, Jobling studied 9 primary tumors of the lungs occurring in 8 mice. All of these animals had neoplasms of other types elsewhere. All of the tumors of the lung were more or less adenomatous, some being more medullary than others. Some were in apparent relationship to bronchioles. Metastases were not found, but there was evidence of invasive growth.

In the first 6,000 mice autopsied from Miss Slye's stock (Slye, Holmes and Wells), 160 mice were found with nodules in the lungs that might fairly be classed as tumors. Twenty of these were classified as highly malignant on the basis of their pronounced heteroplastic character with evidence of active infiltration and the production of secondary growths elsewhere in the lung. The investigators concluded that these tumors of the lungs might have arisen from either alveolar or bronchial epithelium, and that ordinarily the origin of the growth cannot be determined from the character of the epithelium. For the common papillary type, the term "papillary adenoma" was considered more appropriate than "papillary cyst-adenoma." The epidermoid type, examples of which were described by Tyzzer and Haalund, was not represented in this material. Evidence was not found to support the contention that such nodules develop at the site of infarcts produced by nematodes. Of importance, as conclusively demonstrating the malignant nature of certain of these growths, was the discovery of metastases outside of the lung in four instances; to the mediastinal lymph nodes, the chest wall, the diaphragm and the kidney.

Growths of this type, but usually without highly malignant characteristics, are frequently encountered. Those attempting the production of pulmonary neoplasms in mice by insufflation of tar and by other experimental methods must recognize the incidence of spontaneous occurrence (Block and Dreifuss). Bonne found them in both tarred and untarred animals. He stressed the evidence of origin on the basis of an old pneumonia, for it appeared to him that such tumors arose in an area altered by pneumonia and that later the pneumonia completely resolved but the tumor continued to grow.

| Thus, a survey of the spontaneous occurrence of primary epithelial neoplasms in the lungs of lower animals shows that only in reference to mice have there been detailed studies of a considerable number of such neoplasms. The typical form in this animal is entirely different from the form usual in man.<sup>41</sup> The one described for the sheep by Eber was probably of the same type as that found in mice. It is especially striking that tumors in mice arise almost exclusively in the

periphery of the lung while in man a growth radiating from the hilum is the more common. It is also evident that a considerable number of irritative factors are concerned with the production in lower animals of atypical growths in the lungs which often have some, but not all, of the characteristics of true malignant blastomas.

*General Incidence in Man.*—The only important statistical evidence in regard to the incidence of primary carcinoma in man is that based on experience in autopsies. Clinical diagnoses and mortality

TABLE 1.—*The Incidence of Primary Carcinoma of the Lung*

Compiler	Period	Autopsies	Carcinomas	Carcinoma of Lung	Percent- age of Carcinoma of Lung in All Autopsies	Percent- age of Carcinoma of Lung in All Types of Carcinoma
Tanchou.....	Before 1844	.....	8,280	8	.....	0.09
Reinhard.....	1852-1876	8,716	545	5	0.057	0.92
Wolf.....	1877-1884	4,172	.....	9	0.21	.....
Fuchs.....	1854-1885	12,307	.....	8	0.065	.....
Päessler.....	1881-1894	9,246	870	10	0.17	1.83
Wolf.....	1885-1894	7,228	.....	31	0.428	.....
Kikuth.....	1889-1899	13,777	.....	10	0.07	.....
Felchenfeld.....	1895-1900	.....	507	22	.....	5.3
Redlich.....	1900-1905	.....	496	31	.....	6.3
Kikuth.....	1900-1911	22,819	.....	..	0.39	.....
Bejach.....	1908-1913	.....	602	33	.....	4.5
Briese.....	1898-1916	12,971	1,287	60	0.47	4.51
Bilz.....	1910-1919	.....	.....	18	.....	2.57
Barron.....	1899-1921	4,362	.....	13	0.29	.....
Stähelin.....	1900-1924	.....	.....	..	.....	4.0
Berblinger.....	1910-1914	.....	.....	42	.....	2.2
	1915-1919	.....	.....		.....	2.9
	1920-1924	.....	.....		.....	8.3
Lubarsch.....	1920	86,216	8,301	450	0.52	5.4
Kikuth.....	1912-1923	21,588+	.....	146	0.7—	.....
Grove and Kramer.....	1917-1924	3,659	.....	21	0.57	.....
Breckwoldt.....	1914-1925	.....	.....	..	0.33	3.2
Holzer.....	1895-1904	10,167	763	8	0.07	1.04
	1905-1914	9,405	766	13	0.19	2.36
	1915-1924	10,190	733	43	0.47	6.60
Seyfarth.....	1900-1906	.....	.....	307	.....	5.1
	1907-1913	.....	.....		.....	6.88
	1914-1918	.....	.....		.....	11.23
	1919-1923	.....	.....		.....	8.75
6 mo. of 1924		.....	.....	3	.....	15.5
Magarinos and Penna.....	Before 1927	1,531	90		0.195	3.09
Wells.....	1927	.....	403		.....	4.2
Weller.....	1902-1927	2,450	244	10	0.4	4.1
McCræ, Funk and Jackson	1924-1927	621	53	4	0.64	7.5

returns are alike too uncertain to be worth considering. The improvement in the clinical diagnosis of neoplasms of the lung, observable in the past five years, presages a time when such diagnoses will, however, be sufficiently accurate to be of value.

Table 1 includes the more important statistical studies. The arrangement is chronologic so far as is possible. Some overlapping of the years, of course, occurs. The final year of each report determines its position in the table. Some repetitions of data also occur, for successive workers in one laboratory have each incorporated at times data previously used.



This is not the place to discuss the worth of existing statistics of cancer. So many variable factors influence the segregation of human material, as Wells has pointed out, that differences are bound to arise in statistical evidence gathered from various sources. The best evidence at our disposal, however, indicates that, at present, in Europe and in America, primary carcinoma of the lungs and bronchi is found in about 0.5 per cent of all autopsies and in about 5 per cent of all deaths from carcinoma.

*The Trend of the General Incidence.*—Reference to table 1 will show that there has been a change in the apparent incidence of carcinoma of the lung. Prior to 1900, the percentage of incidence of carcinoma of the lung at autopsy ranged between 0.057 per cent (Reinhard) and 0.428 per cent (Wolf). The higher figure was not approached by any other study, yet it is below the probable percentage of incidence at the present time, while the lower figure is about one tenth of the present percentage. This trend has been recognized by practically all who have compiled statistics on this subject since 1900. There is some evidence to show that this apparent increase may have reached a fixed high level or may have fallen off slightly. The experience of the next ten years should settle this point. A summation of statistics by periods compiled by Brunn gave the following result:

From 1872 to 1898, 382,671 autopsies yielded 159 cases of primary pulmonary carcinoma, or 0.04 per cent.

From 1898 to 1916, 192,271 autopsies included 488 cases of primary pulmonary carcinoma, or 0.24 per cent.

From 1916 to 1924, 33,308 autopsies showed 71 cases of primary pulmonary carcinoma, or 0.21 per cent.

The grouping of these cases, made necessary by the use of statistics from various sources, fails to show that it was about the year 1910 that the sharpest rise in incidence occurred.

There can be no question of the apparent increase in the incidence of this condition as shown by the statistics of autopsies, but there is a serious question whether or not this represents an actual increase. Here opinions differ widely (Stähelin, Holzer, Kikuth, Berblinger, Breckwoldt, Briese, Fried and many others). Ewing thinks that the increase in attention to the disease has augmented the number of cases of it recognized. There can be no doubt that this is an important factor, especially as regards reports of isolated cases. The same factor may operate also in large autopsy services in which routine microscopic control is not carried out. The knowledge of the frequency of bronchial carcinoma may lead to that diagnosis being made when in reality the neoplasm of the lung is secondary to some hidden primary growth for which no adequate search has been made. In this connection, Stähelin pointed out that statistics of autopsies are based too often on diagnoses and not on

objective observations; and, further, that diagnoses of carcinoma of the lung made at autopsies are largely institutional diagnoses, and that a knowledge of the diagnostic value of the x-ray and the use of it causes physicians serving homes to send a larger proportion of patients with obscure conditions of the chest into hospitals than was formerly the case.

The factors which have brought about the statistical increase in the incidence of carcinoma in general, such as the shifting distribution of ages in the population, also influence in the same manner the incidence of the condition under discussion. It is rather striking that the proportion of cases of carcinoma of the lung in all cases of carcinoma runs, in practically all statistics, at about ten times the proportion of cases of carcinoma of the lung found at all autopsies. Thus the increase in the number of cases of carcinoma of the lung cannot be explained by the increase in the incidence of carcinoma in general, although influenced by it.

/ If the increase in the number of cases of carcinoma of the lung is only apparent, what were the unrecognized cases of carcinoma of the lung called at autopsy thirty and forty years ago? Some may have been called metastatic neoplasms and others, chronic or fibrocaceous pneumonia. One can be certain that many were called sarcomas. Carcinoma of a relatively undifferentiated type of cell has often passed as small round-cell sarcoma, and areas of spindle cells are frequently seen in bronchiogenic carcinoma (Ewing). As the number of cases of carcinoma of the lung increased, the number of cases of primary sarcoma of the lung decreased, but the total number of cases of sarcoma was not great enough to explain, alone, the changing incidence. 11

Thus one might conclude that the increase in the number of cases of pulmonary carcinoma may be due only to an alteration in the character of our statistics (Fried). If, however, one tabulates the statistics of successive periods in the same institution and that one in which there is continuity of diagnostic standards and often even of personnel, and finds there an increase in the incidence of carcinoma of the lung, one must give the increase more serious consideration. The statistics of nine institutions are presented in this manner in table 2. I can illustrate the method by reference to the results at the University of Michigan, although I realize that here the total number of cases was so small that the effect of chance distribution could hardly be excluded. In the first 1,000 autopsies, only one case of carcinoma of the lung was found (0.1 per cent). In the second 1,000 autopsies, 5 were noted (0.5 per cent). In the first 450 cases of the third 1,000 there have been 4 examples (0.8 per cent). Every autopsy in the series was carefully controlled by complete microscopic study and the directorship of the

laboratory (held by Aldred S. Warthin) remained constant throughout the period represented. Any variable factor must have been inherent in the material itself, either through uneven segregation of the patients in the hospital or through an increase in the number of cases of carcinoma of the lung. I am sure that equally well controlled evidence is available from other institutions included or not included in table 2.

It seems impossible to reach a conclusion on this question at the present time. Sound judgment rests the decision about as expressed by Wells:

TABLE 2.—*The Increasing Incidence of Carcinoma of the Lung in Particular Institutions*

Compiler and Institution	Period	Percentage of Carcinoma of Lung in All Autopsies	Percentage of Carcinoma of Lung in All Types of Carcinoma
Reinhard (Dresden); Wolf (Dresden).....	1862-1876	0.057	.....
	1877-1884	0.21	.....
	1885-1894	0.428	.....
	1895-1900	0.07	.....
Kikuth (Hamburg-Eppendorf).....	1900-1911	0.39	.....
	1912-1923	0.7— (?)	.....
	1914-1919	0.36	3.7
	1920-1925	0.39	2.7
Seyfarth (Leipzig).....	1900-1906	.....	5.1
	1907-1913	.....	6.88
	1914-1918	.....	11.23
	1919-1923	.....	8.75
	1st half 1924	.....	15.6
Stähelin (Basel).....	1900-1911	0.29	.....
	1912-1914	0.50	.....
	1915-1923	0.63	.....
	1924	0.67	.....
Holzer (Prague).....	1895-1904	0.07	1.04
	1905-1914	0.19	2.36
	1915-1924	0.47	6.69
Barron (Mayo).....	1899-1911	0.0	.....
	1912-1918	0.2	.....
	1919-1921	0.0	.....
Assmann (Leipzig).....	1900-1906	0.67	5.01
	1907-1913	0.9	6.88
	1914-1918	1.01	11.23
	1919-1922	1.54	9.17
Weller (University of Michigan).....	Autopsies		
	1-1,000	0.1	.....
	1,000-2,000	0.5	.....
	2,001-2,450	0.8	.....

\* There seems to be little doubt that primary cancer of the lung is now a more common disease in Europe and America than it was even ten or fifteen years ago. . . . Perhaps there are changes in the incidence of cancer, independent of the increased age level of the population. . . . I am not by any means sure that changes of habits and occupations may not be having some influence on the incidence of cancer.<sup>11</sup>

If one grants for the time being that the increase in the incidence is in part real, possible factors which may be concerned in this increase will be considered under the head of "Etiology."

*Incidence According to Sex.*—Breckwoldt, summarizing sixteen of the more recently reported series of cases of primary carcinoma of the

lungs, found that 807 cases occurred in men and 280 in women. This corresponds to a ratio of 2.8:1. None of the compilers of the sixteen series found a preponderance of cases in women even in relatively small series, and only one (Marchesani) found an equal involvement of the two sexes. In 1913, I collected from the literature and studied a group of eighty-seven cases of microscopically verified primary carcinoma of the larger bronchi. Seventy of the eighty-seven were in men. Due allowance having been made for some preponderance in the number of male patients in the hospitals from which many of the statistics are derived, it is clear that primary carcinoma of the lungs is about three times as frequent in men as in women. It likewise plays a more important rôle in men than in women when compared with carcinoma at other sites. Lubarsch found in a series of 86,216 reports of autopsies collected from all Germany that carcinoma of the lung comprised 8 per cent of all cases of carcinoma in men and only 2.57 per cent of all cases in women. Further studies of great interest can be undertaken to discover whether this predisposition for a given sex is equally evident in all types of carcinoma of the lung.

*Incidence According to Age.*—When, in 1913, I plotted the incidence of eighty-five cases of primary carcinoma of the larger bronchi according to the ages of the persons involved, I found the highest point of the curve in the age period from 56 to 60. This highest point represented seventeen cases. A subsequent study of 1,100 microscopically verified cases of operable carcinoma in general showed that when the curve of incidence of this material was corrected for the constantly declining population of aged persons its apex fell in the quinquennium from 58 to 62. From this, it followed that the incidence of bronchial carcinoma according to age was in close accord with that of carcinoma in general.

The larger statistical studies of more recent years reached substantially the same result. Holzer found his cases distributed in periods as follows: from 20 to 30 years, 1; from 30 to 40 years, 10; from 40 to 50 years, 18; from 50 to 60 years, 30; from 60 to 70 years, 12, and from 70 to 80 years, 5.

Breckwoldt found 30 of 47 cases in the period from 50 to 70, with 15 cases in each decade. The cases analyzed by Kikuth were grouped in periods as follows: from 20 to 29 years, 7; from 30 to 39 years, 18; from 40 to 49 years, 49; from 50 to 59 years, 77; from 60 to 69 years, 60; from 70 to 79 years, 30, and at 80 years and over, 5.

In Brunn's grouping of collected cases by twenty-year age periods, the results were: from 1 to 20 years, 7 cases; from 20 to 40 years, 60 cases; from 40 to 60 years, 361 cases; from 60 to 80 years, 144 cases, and at 80 years and over, 4 cases.

To all of these larger series many microscopically unverified cases were admitted. While most cases of carcinoma of the lung occur at



the "cancer age," occasionally cases are seen in the extremes of life, and apparently in about the same relative frequency as cancer of the stomach, the uterus and the breast.

*Incidence According to Occupation.*—Pulmonary carcinoma affords in the "Schneeberg lung-cancer" what is probably the most extraordinary and at the same time the least understood of all the associations which have been discovered to exist between occupation and the incidence of neoplasms. For centuries it has been known (literature reviewed by Härtwig and Hesse; Arnstein; Uhlig; Rostoski, Saupe and Schmorl and others) that a considerable proportion of the underground workers in the cobalt mines of the Schneeberg district in Saxony have, in each generation, died in middle life from some pulmonary disease. The literature on this condition begins at least as early as 1500. The picture of the disease seems not to have varied through the centuries, being characterized by cough; mucoid, mucopurulent or bloody sputum; progressively increasing dyspnea; loss of weight and strength; tendency to sweating; boring pain in chest or back, and death after a varying period of incapacity. There is no way of ascertaining what proportion of those working developed this condition. From local records, however, it appears that during the latter part of the nineteenth century, when from 500 to 600 men were employed in the mines, the number invalided or dying from cancer of the lung varied from none to sixteen per year (Uhlig). From 1907 to 1911, local death registers gave diseases of the lungs as the cause of 44 per cent of all the deaths of miners (Arnstein). These must have been minimal figures since there practically were not any autopsies. In recent years the number employed has greatly decreased but there is now more accurate information as to the incidence of the condition in question. In the course of the official investigation (three and a quarter years) which formed the basis of the studies of Thiele, Schmorl, Rostoski and Saupe, 154 miners were studied by the methods of modern clinical diagnosis, including roentgenoscopy. During this same period, twenty-one of these died and for thirteen a diagnosis of carcinoma of the lung was established by autopsy, that is, for 62 per cent. For two of the eight on whom autopsies were not made, the diagnosis of carcinoma of the lung was considered highly probable. When these are included the percentage becomes 71. Two of those in whom carcinoma was found at autopsy had not worked in the mines for many years, although at an earlier period one had been so employed for ten years and the other for seventeen. If these two are excluded as not being 'miners,' together with the two whose cases were not verified by autopsy, there still remain 52 per cent of all the miners examined, whose deaths are chargeable to carcinoma of the lung.



In the course of the same investigation, 362 persons of the same districts, but not employed in the mines, were examined without the finding of a single example of carcinoma of the lung.

"Schneeberg lung tumor" was incorrectly interpreted as to its neoplastic type for many years; for the earlier workers believed it to be a "sarcoma," "lymphosarcoma" or "lymphosarcoma fibromatodes," being governed by the same error that has occurred so frequently even in recent years in connection with the undifferentiated type of carcinoma of the lung. Lord, even in 1925, continued to class the Schneeberg tumor as lymphosarcoma. One of the cases studied by Arnstein was a squamous cell carcinoma, which left no doubt as to its epithelial character. Of the 21 cases examined post mortem which Schmorl found available for study, the condition occurred on the left side in twelve and on the right side in nine. In twelve cases, carcinoma of squamous cell type was found, in seven of which it was cornifying. Six cases were of the type of a relatively undifferentiated carcinoma simplex.

Schmorl concluded as a result of the investigation with which he was associated that cancer of the lung is still endemic in the Schneeberg district, that the condition is one of true epithelial neoplasia, and that it occurs only in the miners themselves or in those in the most intimate contact with the products of the mines. (The various theories as to the etiology of this condition are discussed in the appropriate section under the head "Etiology.")

Adequate study has not been made as to the general influence of occupation on the incidence of carcinoma of the lung. Seyfarth noted that it is almost exclusively a disease of laborers and handworkers, occurring with special frequency among cigar makers, metal workers, type setters and printers. Five of Kikuth's 246 cases were in cigar makers. To this list Marchesani and others have added cases in coal miners and coal mine laborers, sand stone workers, felters, etc. One can pick out from the lists of cases in persons of known occupation those which may be of significance, but at present a method of evaluating such isolated observations has not been devised. Such cases as that reported by Boyd in a bottle-blower or those described by Beck, Georgi and Wolf in blacksmiths, by Handford in a collier, by Geipel in a cigar maker, by Scott in a chemist in a smelter, by Bryan in a laborer in a smelter, by Kikuth in a chemist, by Fuller in a laborer in a gas works and by Gutzeit in a glass maker may well be of significance. Klotz found that most of the twenty-four cases of which he had personal knowledge occurred in members of the laboring class engaged in diverse occupations. One was in a miner, two were in glass workers and another was in a metal polisher. One gains the impression that such laborers and artisans are especially predisposed, and that members of the learned professions are relatively immune in respect to carcinoma of the lung.

## ETIOLOGY

It is not possible to arrange an ideal classification to include all of the possibly predisposing factors which have been thought to influence the occurrence of primary carcinoma of the lung. / In a rather rough way, those which have been suggested may be grouped under the following five heads: tuberculosis; mechanical trauma; acute and chronic infections, fibroid pneumonia and bronchiectasis, of bacterial origin; chronic irritation, chemical, mechanical, thermal and radioactive; and intrinsic predisposition. "

*Tuberculosis.*—This condition should be given separate consideration, because it was early considered the chief etiologic factor, and Ewing still states that such is the case. / This belief was established by Wolf's series in which 13 of 31 cases were associated with tuberculosis and has been kept alive by occasional examples of squamous cell carcinoma arising in bronchiectatic cavities associated with chronic pulmonary tuberculosis, such as the early observation of Friedländer, and by other examples of the coincidence of the two conditions. " A rather impressive list of examples of the latter type could be compiled from the literature (reviewed by Kikuth) / but it must be borne in mind that two conditions which are so common must often be concomitant without implying a causal relationship. " It is significant that carcinoma of the lung appears to be increasing at a time when pulmonary tuberculosis is decreasing throughout the civilized world. " Kikuth found tuberculosis mentioned but 22 times in his series of reports of 246 cases of primary carcinoma of the lung. This is roughly in accord with the known incidence of tuberculosis in unselected series. Kikuth felt that tuberculosis plays a small rôle, if any, in determining a malignant pulmonary condition, occupying in this respect exactly the same position as a considerable number of other chronic inflammatory diseases. This is the prevailing opinion at the present time.

*External Mechanical Trauma.*—Aufrecht considered severe trauma which "does not produce laceration of the pulmonary tissue, but only molecular disturbances of an unknown character" to be an important immediate cause of pulmonary carcinoma. " Four cases which he had seen were preceded by grave trauma. One woman died of carcinoma of the right lung sixteen months after falling from a ladder and striking the right side of the chest. A man accidentally received the full weight of a beam, which he was assisting in lifting, on his left shoulder. Two years later he died of diffuse carcinoma of the upper lobe of the left lung. Georgi's blacksmith was hit on the chest by a heavy mass of iron. The third patient described by Scott and Forman had suffered severe contusions of the chest when caught in a belt. The carcinoma, however, developed on the opposite side. In Barron's fifth case the patient gave

a history of a fall from a ladder, striking the chest on a plank, shortly before the onset of pulmonary symptoms. Similar examples are to be found here and there throughout the literature (Hinterstoissen, Handford) but they are so few that one must conclude, contrary to Aufrecht, that a single episode of external mechanical trauma is practically not of importance in determining carcinoma of the lung.

*Acute and Chronic Infections: Fibroid Pneumonia and Bronchiectasis, of Bacterial Origin.*—The apparent rise in incidence of malignant pulmonary conditions following the great influenza epidemic of 1919-1920 attracted attention to a possible causal relationship between the two conditions. Meyer does not hesitate to explain his case thus. As will be pointed out under the head "Histogenesis," metaplasia of the bronchial epithelium to the squamous cell type is an undoubted forerunner of bronchial carcinoma in certain cases. Mittasch, Askanazy and others have found such changes in cases of influenza, but Koopmann did not find a single case of epithelial metaplasia or of atypical proliferation in a relatively large series. Whatever effect influenza may have would seem, therefore, to depend on chronic inflammatory processes, residual to the sequelae of influenza, rather than on influenza itself. Nevertheless, as I know from personal experience, it is the custom in certain European institutes to assign the apparent increase in the number of cases of carcinoma of the lung to this one cause. There is good evidence to show that its effect cannot be very weighty. Kikuth found reference to a preceding influenza in only 21 of 246 reports of cases of carcinoma, and in these the interval of time intervening varied from three months to ten years and over. The literature dealing with this question is concisely reviewed by Hueper. He pointed out that no similar increase was noted after the pandemic influenza of 1889-1894, that the present trend of increase was already apparent before 1919-1920, that even the most enthusiastic advocates are unable to show any considerable incidence of "influenza" for their cases of carcinoma of the lung, and finally that the contrast between the two conditions in respect to incidence according to sex is an important objection to this theory.

The sequelae of influenza, however, so far as they bring about bronchiectasis or chronic fibroid pneumonia, are of importance. There are many examples of carcinoma of squamous cell type, arising in bronchiectatic cavities, a few in supposed syphilitic scars (Ziemssen) and several in areas of fibrosis. The writer has seen carcinoma of the lung in association with chronic fibroid pneumonia in which the transition pictures between the regenerated bronchiolar epithelium (cells of Tripier) and undoubted neoplasm did not leave any question of the origin of the malignant process in the area of induration. Such chronic

inflammatory conditions as are accompanied by metaplasia or excessive regeneration must be included among the predisposing factors.

*Chronic Irritation; Mechanical, Chemical, Thermal and Radioactive.*

—In considering this group of factors, which have assumed great importance in the last few years, attention must first be directed to two lines of evidence which are instructive in their bearing on the whole problem. The first of these has to do with the many theories which have been advanced to explain the etiology of the carcinoma of the lung in the miners of the Schneeberg. The theories show how complex, in reality, is an industrial hazard which appears to be of relatively simple solution. What environmental factor predisposes the Schneeberg miners to carcinoma of the lung? This subject has recently been thoroughly reviewed by Rostoski, Saupe and Schmorl. In part, these mines are damp and show abundant growth of both microscopic and larger fungi. The men are compelled to climb up and down ladders for considerable distances, in some instances for as much as a thousand feet. In the harder rock, where drilling is necessary, a fine stone dust is produced in quantity. The ore contains iron, bismuth, tin, zinc, lead, manganese, uranium, cobalt and nickel, chiefly in combination with sulphur and arsenic. The ore is also radioactive. Thus the situation affords the possibility of mechanically irritating stone dust, chemically active dusts, particularly arsenic, the possibility of inhalation of arsine, diethylarsine, or other volatile arsenic compounds, perhaps produced by the flora of the damp mines, and the inhalation of a radioactive substance. The rock dust actually has at times a content of arsenic of nearly 0.5 per cent and prolonged contact with it leads to a chronic eczema. The air of the mines has a radioactive emanation content of from a few to 50 Maché units. Schmorl felt that the anthracochalcosis found in the lungs of these miners must be of significance. Pneumokoniosis was demonstrated by the x-ray in many of the living. Yet such a mechanical irritation fails to explain why in this group of mines, alone, carcinoma of the lung has been prevalent for centuries. The final answer is still to be sought. Sanitary measures looking toward a reduction of the dust hazard seem already to have effected some reduction in the incidence of the disease. The mines, however, are now being worked on a much smaller scale.

The second line of evidence to which attention must be called is the experimental production of new growths in the lungs of laboratory animals. Following the introduction of dilute hydrochloric acid into the bronchial tree, Winternitz, Smith and McNamara found that an "overproduction of the epithelium occurs and may form bronchiolar polypi or extend into the peribronchial tissue" producing a picture which "may easily be confused with that of a malignant neoplasm." This is probably the basis of a statement frequently quoted in the German literature that



bronchial carcinoma was thus produced by them (Joannović). Kimura quotes Ibuka as having introduced pieces of paraffin into the lungs of rabbits. These became encapsulated by much scar tissue in which, in three instances, epithelial tubular and alveolar structures were formed, but not anything that could be interpreted as cancer. Block and Dreifuss, in 1922, were successful in producing skin cancrioids in mice by "tarring." Four fifths of the mice with the skin cancrioids showed metastases to the lung. Two or three mice presented, in addition, adenomatous tumors of the lung of the usual type, but these were thought to be spontaneous and not in any sense due to the tar and tar derivatives which were being tested.

By intrabronchial insufflation of coal tar, Kimura produced in the lung of a rabbit a small, circumscribed nodule consisting of twisted tubules lined by an epithelium of cylindric cells, an adenoma-like growth. In a guinea-pig which had been thus treated and killed on the 140th day, multiple nodules were found in the lungs. One hard mass, of the size of a large pea, was composed of groups of epithelial cells with a glandular architecture. Bronchi and bronchioles were embedded in the tumor mass. The epithelial lining of these bronchi was several times as thick as the normal lining and there were polypoid ingrowths partially occupying the lumen. The boundary of the mass was not well defined, and it seemed to infiltrate the surrounding lung tissue in a radiating manner. This was interpreted as adenocarcinoma of bronchial origin, produced by chemical stimulation alone, in an animal possessed of a special predisposition.

Murphy and Sturm endeavored to eliminate the criticism that the tumors of the lung in tarred animals are but the metastases of unrecognized primary carcinoma of the skin by applying the tar to twelve different areas on each mouse. Tumors of the lung of the usual type for mice were found in 60 per cent of the animals in one series and in 78.3 per cent in another. "Control mice from the same stock, but from three to six months older, and for that reason the more liable to spontaneous lung tumors, failed to show a single instance of such growths." It was believed that the inhalation of particles of tar could be ruled out as a cause.

In 1925, Möller produced in 6 of 24 rats, treated on the skin of the back with tar, primary cornifying squamous-cell tumors of the lungs. All of the rats, and those only, which survived to receive treatment for 300 days or more, developed these growths. Microscopic examination of the treated areas of the skin failed to show a neoplasm.

In thirty-one mice dusted daily or every other day with a dried pulverized tar gum arabic emulsion, and 104 mice which were tracheotomized and into which a fresh tar gum arabic emulsion was injected (once only) intratracheally, Bonne did not find a definite increase in



the incidence of tumors as compared with untreated animals. One of twenty rats tarred about the mouth twice weekly for twenty weeks was found to have two nodules the size of pinheads at a lung border. Histologically, these were cornifying squamous cell carcinomas. Association with a bronchus could not be demonstrated.

In the present year (1928), Willis and Brutsaert have described tumor-like structures in the lungs of guinea-pigs exposed to silica dust. In 7 of 80 guinea-pigs which were exposed for from eighteen to thirty-one months for periods totaling about fifty hours a month to the inhalation of a dust which was 98 per cent silicon carbide, remarkable peribronchial proliferations were found. These appeared to be derived from both bronchial and alveolar epithelium and were found only in the "dusted" animals. Positive evidence of adenocarcinoma character was lacking.

From this survey it may be seen that some success has been obtained in producing tumor-like structures in the lungs of laboratory animals, particularly mice. Tar and tar derivatives have been the most successful aids in bringing this about.

Returning to a consideration of the etiology of carcinoma of the lung in man, one finds that a great variety of irritative agents have been suggested. Space does not permit a review of the discussion, pro and con, which has developed in respect to each of these. The first was anthracosis, early suggested by Wolf as being important in connection with the breaking through to the bronchial mucosa of pigment-laden bronchial nodes. Industrial dusts have also received much attention, particularly, among the organic dusts, tobacco. The number of cigar-makers affected by pulmonary carcinoma has seemed disproportionate to the number engaged. Of the inorganic dusts, the silicates (silicosis) have been especially considered, and certain industrial metallic dusts. On the importance of excessive cigarette smoking, Fahr is quoted by Hueper. Perret and others have been struck by histories of excessive use of tobacco in their patients. If this be the true explanation, there should be an alteration of the present ratio of the incidence in men to that in women within the next decade or two. Specific chemical fumes seem to have played a part in many cases. Chemists and those working about smelters appear rather frequently in the lists of cases of carcinoma that have been classified according to occupation of the persons involved. Kikuth was much impressed by the case of a young man aged 39, previously healthy, who died of bronchial carcinoma fourteen months after going to work in a chemical factory in which he was exposed to heavy fumes containing dichlorethylene, trichlorethylene, pentachlorethane and hexachlorethane. The gassing of men in the war has also been considered a factor in increasing the incidence; and in view of the coincidence of the increase in the incidence of carcinoma of

the lung with the increase in the use of automotive vehicles, the products of the incomplete oxidation of gasoline and other motor fuels must be included among the possible etiologic factors. Stähelin has investigated particularly the use of tar and heavy oils in laying street dust, since particles coated with these materials must be constantly inspired in the course of the abrasion of such roads. Here there is an important field for further study. At present, it is not clear that there is any close parallelism in various cities between such laying of dust and malignant conditions of the lungs. The diagnostic and therapeutic use of the x-ray has been considered, but it seems rather clear that this can be dismissed as a causative factor, although important in centralizing these cases in institutions. Discussions of these factors with reference to the views of the chief proponents of each can be found in articles by Kikuth, Berblinger, Hueper, Stähelin, Marchesani, McCrae, Klotz and others. In a general article on neoplasia of irritative origin, Joannović wrote in regard to the group under discussion:

The more or less constant inhalation of finely divided vegetable dust appears to be the cause of cancer of the respiratory tract in cattle, sheep and horses. The remarkable increase in pulmonary cancer in man has been variously ascribed by authors to metaplastic epithelial proliferations secondary to influenza, to war-gassing and to the abuse of cigarette smoking. Upon the ground of various observations one is more and more inclined to attribute to the inhalation of dust and the resulting pneumokoniosis a greater significance in the origin of pulmonary cancer.

Final conclusions cannot be drawn at present, but many interesting fields have been opened for further study.

*Intrinsic Predisposition.*—Most writers on the subject dismiss with a brief negation the possibility that an inherited predisposition is of importance in the etiology of carcinoma of the lung. That this should not have received fuller consideration is all the more remarkable since the tumors of the lung in mice have played an important part in the experimental proof of the importance of hereditary factors as this has been developed by the work of Slye, Tyzzer, Lynch and others.<sup>11</sup> Experimenting pathologists and geneticists, no matter how much they may differ in regard to the mechanism involved and its mendelian implications (recessive, sex-linked dominant, dominant), are agreed that it is possible largely to determine the incidence of tumors of the lungs in mice by proper selective breeding.<sup>12</sup> With this important lead, it is surprising that the reports of cases and the statistical studies of carcinoma of the human lung practically never mention a family history of malignant conditions whether it be negative or positive. There are a few exceptions. For instance, Moise emphasized the strong family history of malignancy in his case 4. The patient was a woman, aged 42, whose father had died of cancer of the liver, paternal grandfather

of cancer of the stomach, a paternal aunt of cancer of the breast, and whose sister had had a renal tumor of unknown nature removed. The father of a patient, a woman 31 years old, described by Bergmark and Quensel, died of intestinal carcinoma at 32. Such reported histories are few, but apparently this point has not been adequately investigated.

*Summary of Etiology with Probable Trend of Opinion.*—If one may be permitted to look ahead in the light of recent advances, it may be predicted that the development of carcinoma of the lungs and bronchi will be found to be due (1) to an inheritable intrinsic predisposition which may be activated by (2) a variety of chronic irritative factors. These may be mechanical, chemical, bacterial, thermal or radioactive, but they have in common the ability to incite proliferation of certain cells, regeneration, repair, hyperplasia and often metaplasia. Such extrinsic factors are potent in the production of pulmonary and bronchial carcinoma in varying degrees in different persons depending on the degree of intrinsic predisposition which may be present.

#### GROSS PATHOLOGIC ANATOMY

*Location.*—Carcinoma of the lung is, in a majority of instances, carcinoma of a bronchus. "Bronchiogenic carcinoma" has become a common diagnostic phrase with the realization of this fact. Kikuth believed that 179 of the 225 cases studied by him were definitely of bronchial origin. Breckwoldt found 36 of the bronchial form out of a total of 47. The actual proportion is undoubtedly higher, as each of these writers had a fairly large group of doubtful cases, some of which were probably bronchial. In 1913, I collected and reported on a group of carefully selected cases of carcinoma of the larger bronchi, hoping to establish such a definite clinical picture for this condition that it could be set off from the general group. This hope has been realized only partially, on account of the fact that proved cases of nonbronchiogenic carcinoma of the lung are rare indeed. Certainly, the ratio must be as high as ten bronchiogenic to one of other origin.

In the older literature and in textbooks, stress has been laid on a supposed excess of cases of carcinoma in the right lung as compared with the left. Reinhard, for instance, in 1878, reported 18 instances of carcinoma for the right lung and but 9 for the left. This disproportion was attributed to the larger size and more direct course of the right main bronchus in the thought that it would be subjected to a greater degree of chronic irritation than the left. Adler, in his combined list of parenchymal and bronchial neoplasms, found the right side more frequently affected than the left, but thought the difference was too small to serve as a basis for a theory. In more recent statistical studies, the difference between the two sides in respect

to incidence of carcinoma has not been evident. Kikuth found the right lung primarily involved in 123 instances, the left in 118, and an equal involvement of both lungs in 5. In summing up 503 unilateral cases, including forty-three of his own, Breckwoldt found the right side primarily involved 273 times; the left, 230 times. This slight right preponderance is rather constant in the collected series of recent years, only a few writers—among others, Schmorl with the Schneeberg miners, and Hanf—seriously differing. The latter found 95 cases of carcinoma of the left lung to 72 of the right. In the compiled series of McCrae, Funk and Jackson there was a slight preponderance of cases of carcinoma of the left lung. Brunn found, on combining 252 additional cases, chiefly from the literature, with Adler's list of 374, that 283 were said to be of the right side, 246 of the left side, 26 of both sides, with 3 doubtful and 68 in regard to which no statement as to side was made.

As to lobar distribution, a grouping which necessarily excludes many tumors of the hilum, Kikuth found the right upper and middle lobes involved 38 times; the right lower lobe, 35 times; the left upper lobe, 31 times; and the left lower lobe, 30 times. In addition, there were 49 instances in which all three lobes on the right were involved and 57 in which both lobes of the left lung were involved. Breckwoldt likewise found the right upper lobe to be involved slightly more frequently than any other single lobe.

*Types.*—Numerous classifications of carcinomas of the lung have been proposed. A survey in the light of the hundreds of reports of cases now available shows that from the standpoint of gross pathology, three types must be considered: a type associated with the hilum, a nodular type developing in the parenchyma of a lobe and a diffuse type. Evidence is lacking that the alleged primary miliary carcinoma reported by certain writers is other than metastatic miliary carcinomatosis with an undiscovered primary. Pleuritis carcinomatosa (Bergmark and Quensel) is but a manifestation of carcinoma arising elsewhere, either within the lung or outside of it. This grouping agrees as to its three main types with that proposed by Fishberg for his series of neoplasms of the lungs.

The type of carcinoma that occurs in the hilum, comprising perhaps 90 per cent of all cases of carcinoma of the lung, is practically always bronchiogenic. It may arise in a main bronchus at or near the bifurcation and thus be originally outside of the boundary of the lung itself. A frequent site is in the main bronchus near the mouth of the first lobar branch (Kikuth). The gross appearances as seen from the lumen are exceedingly variable, ranging from a roughening of the mucosa, through various types of intrabronchial polypoid masses (literature reviewed by Kirch) to complete bronchial stenosis, which is not infrequently present



when the condition is seen at autopsy. In the bronchial wall, the neoplasm infiltrates widely, extending along the bronchial tree and radiating into the substance of the lung and also into the mediastinum. Death may occur while an intrabronchial mass is still small or only when an enormous neoplasm fills the mediastinum and nearly completely replaces the lung. With the more massive examples of this type, the bronchi, when cut across, are found completely infiltrated and their lumina plugged. The neoplasm is usually firm in consistency, except where showing secondary necrosis, and is yellowish white. With secondary infection or extensive necrosis, cavitation of the neoplasm occurs.

The nodular type, developing in the substance of a lobe, is much less common, yet there are many descriptions of it in the literature. When such nodules are described as multiple, there must always be some suspicion that the condition is not primary in the lung. Certain cases, however, seem well authenticated. Schmorl saw multiple foci of origin in one or two of the Schneeberg cases which he investigated. McMahon and Carman found multiple nodules in both lungs of one of their patients (109685) and did not find any evidence of a primary growth outside of the lung. Such a picture might be explained as one of intrapulmonary metastasis from a single primary. Another possible source of error in connection with this variety can be illustrated by Brunn's second case in which x-ray showed a circular tumor-like mass in the lung in the left infraclavicular region. This was removed and diagnosed as papillary adenocarcinoma. At autopsy ten days later, a small tumor practically filling a bronchus near the root of the lung was discovered, but the apical mass was nevertheless considered to be the primary tumor. It seems more probable that the tumor in the hilum was the original one. As will be pointed out later, the lobar situation of a carcinoma does not exclude a bronchial origin. A tumor described by Edlavitch lay chiefly in the right apex, bulging the clavicle forward, yet it was of undoubted bronchial origin.

An extensive literature has arisen in respect to the diffuse type, which is frequently bilateral. Here, again, suspicion is justifiable that the pulmonary condition may be metastatic from a hidden primary, but there are now many cases which have been well studied so that this type must be given serious consideration. The unilateral manifestation of this condition can be illustrated by the instance observed by Gordon. The patient was a woman, aged 56, who had had for four months a cough, dyspnea, a little expectoration, but no hemoptysis. At autopsy, all of the right lung with the exception of the inferior portion of the lower lobe was found infiltrated with a homogeneous mass.

Grossly, the condition looked like the gray hepatization stage of croupous pneumonia. Signs of disease were absent in the other organs.



Microscopically, each alveolus was found to be filled with a "papillomatous collection of columnar epithelial cells arranged on a delicate fibrous support of dendritic structure." The bronchi were unaffected.

The bilateral form of this type was described by Musser in 1903 as it was found in a man, aged 47. "Uniformly throughout both lungs, affecting all parts, is a diffuse grayish-yellow infiltration." Microscopically, the alveolar architecture of the lung was more or less retained and papillary ingrowths covered with cubical or columnar cells were everywhere found projecting into the alveoli. Prostate, thyroid and all other organs were examined without finding a primary outside of the lung. Bryan, Eismayer, Briese and many others have described similar examples. Briese reviewed a number of additional cases falling into this group. The case described by Hyde and Holmes gave clinical and roentgenologic evidence of involvement of the right side first, while at autopsy, eight months later, both lungs were found to be extensively infiltrated with no evidence of an extrapulmonary primary. This case affords a possible explanation of the bilateral form of the diffuse type, for metastatic dissemination throughout the lungs seems more probable than does such extensive multicentric origin.

Forms representing transitions between these three main types are occasionally encountered, and when the neoplasm has infiltrated extensively it may be difficult of classification.

*Regional Extension.*—Particularly in the type associated with the hilum the mediastinal extensions become important. Certain structures are involved with great frequency. The pericardium and heart are more frequently infiltrated when bronchiogenic carcinoma is present than in the case of any other form of neoplasm. Brunn found the heart involved in 21 per cent of 626 reported cases. In the literature, the process is frequently called metastasis but it is usually a direct extension through the pericardium, in the perivascular lymphatics or along the lumina of the great vessels themselves. A frequent reference in the literature is that to a polypoid neoplastic mass protruding into the right auricle from the mouth of the superior vena cava or into the left from a pulmonary vein. The myocardium may be infiltrated nearly to the apex (Young).

An extension to the great vessels of the thorax is also common. It may occur as a compression and infiltration of the wall, or more commonly as a so-called neoplastic thrombus filling the lumen. The superior vena cava, the pulmonary veins and the pulmonary arteries are most frequently concerned. Caval obstruction leads to vascular changes, to be described shortly. Several cases are reported in which death occurred through massive hemorrhage from an eroded pulmonary artery (Kikuth, Moses, Bruecken discussing the paper of Dever and Royce).

The esophagus is frequently compressed and infiltrated, usually in its middle third. This may produce marked dysphagia. The compres-

sion of the trachea gives the "cornage" sign of the French. The compression and infiltration of regional nerves leads to recurrent laryngeal paralysis, to pupillary inequality and to pain along the intercostals. The frequency of the involvement of the nerves is shown by the fact that thoracic, abdominal or back pain occurs in over 50 per cent of all cases.

A direct extension to the thoracic wall is more rare. Bruecken, in discussing the paper of Dever and Royce, described a patient on whom a diagnosis of gumma of the sternum, and later of sarcoma of the sternum had been made. Autopsy showed this lesion to be a direct extension of a squamous-cell carcinoma of the right bronchus. Kikuth found a mass the size of an apple in the left pectoralis muscle in continuity with a primary carcinoma of the lung.

*Metastasis.*—Carcinoma of the lung rarely fails to produce metastases. In the series compiled by Klotz, metastasis was absent in only one instance and Breckwoldt found metastases in 37 of 43 cases. The regional lymph nodes are involved in practically all cases: the bronchial, supraclavicular, cervical and axillary. In many cases, the removal of a node for microscopic examination has confirmed the diagnosis. After the regional nodes, Kikuth found metastases to be distributed to the other organs, in his series of 246 cases, as follows: liver, 70; skeleton, 48; lungs, 43; brain, 31; kidney, 25 (left, 9; right, 4; both, 12); suprarenals, 21 (left, 8; right, 4; both, 9); pancreas, 11; thyroid, 5; heart muscle, 4; intestines, 3; stomach, 2; spleen, 2; gallbladder, 1, and ovary, 1.

Dosquet has studied the distribution of the metastases from primary carcinoma of the lung, including bronchial carcinoma, from the standpoint of the preponderance of suprarenal and central nervous system metastases, which this condition produces. He found in a group of 105 cases of carcinoma of the lung that 31.4 per cent showed metastases to the central nervous system and 21.8 per cent suprarenal metastases. When other forms of cancer were brought into comparison, 2,158 cases showed 0.9 per cent with metastases to the central nervous system when the lung was not involved, and 1.6 per cent when the lung was involved, a total of but 2.5 per cent. Similarly, the same 2,158 cases of carcinoma yielded 1.9 per cent with suprarenal metastases when the lung was not involved, and 2.6 per cent when the lung was involved, a total of 4.5 per cent.

The frequency of metastases to the central nervous system as found at autopsy (Fried) is paralleled by the frequency of clinical cases in which such metastases dominate the picture and lead to erroneous diagnoses. Apoplexy and tumor of the brain (Lubarsch) have frequently been diagnosed, sometimes on the basis of hemiplegia.

The skeletal metastases have never been fully studied, and their importance should be emphasized. In the usual autopsy, most

bone metastases escape detection. A suddenly developing vertebral deformity, as in the thirteenth case in Barron's list, may be the first indication of such a disease. The Department of Pathology of the University of Michigan has in its series a similar example in a patient with a diagnosis of Pott's disease, which proved to be metastatic carcinoma from the lung.

*Changes in the Lung, Peripheral to the Carcinoma.*—The common bronchiogenic type is often accompanied with important changes in the lung, peripheral to the neoplasm. These are determined largely by the degree of obstruction and, when present, they influence the physical signs of the disease. With a polypoid growth into the bronchus, a ball-valve action may be present, so that there is emphysema peripheral to the neoplasm. Atelectasis due to obstruction is more common. Körner described a case of atelectasis due to a complete obstruction of the entire right lung by a bronchiogenic carcinoma, which was present, moreover, for seven weeks before the death of the patient. In a personal communication, C. H. Cocke provided me with notes on another as yet unpublished case of massive collapse of the right lung due to a malignant endobronchial neoplasm. Bronchiectasis with chronic purulent bronchitis frequently occurs beyond the region of the neoplasm, and an entire lobe or the greater part of the lobe may show a chronic fibroid pneumonia.

*Pleural Effusion.*—The pleura is usually involved in the carcinomatous infiltration by the time death occurs. There may be a general pleuritis carcinomatosa, as described by Bergmark and Quensel, or the pleural involvement may be more nodular in type. Kikuth found in more than half of his cases an exudative pleuritis, which was of a hemorrhagic character (twenty-eight instances). Diagnosis from cells in the pleural fluid is discussed in a subsequent section.

*Vascular Phenomena.*—Changes in the flow of the blood and the lymph, particularly of the upper part of the body, are responsible for an interesting chapter in the pathology of carcinoma of the lung. These depend on compression, infiltration and blocking of the greater thoracic vessels by the tumor. The inequality of radial pulses may be due either to intrathoracic pressure from the primary tumor or to axillary metastases. Its presence may induce an incorrect diagnosis of aortic aneurism. Venous engorgement, often with marked cyanosis and edema, is more common. Fishberg's experience was unusual, for he saw such signs of distant pressure in but 2 of 60 cases of primary malignant disease of the bronchi, lungs and pleura. In 90 reported cases taken at random from the literature, some of which were incompletely described, I found such venous phenomena referred to 8 times. Nonnenbruch emphasized unilateral inspiratory distention of the veins of the neck as a diagnostic sign of stenosis due to bronchial carcinoma. This sign is

observed on the side opposite the neoplasm. Dana and McIntosh, in 1922, surveyed the diagnostic significance of venous obstruction in carcinoma of the lung, particularly in respect to the superior vena cava. The seat of the malignancy was found to be in the right lung or bronchus in most of these cases. One patient in my own series showed an extraordinary distention of the superficial collateral veins of the anterior thoracic and abdominal wall. At autopsy, a tumor was found completely blocking the superior vena cava.

*Clubbing of the Fingers, Osteo-arthropathy.*—In 1915, Locke concluded that simple clubbing of the fingers and secondary hypertrophic osteo-arthropathy should be considered as identical, the former representing an early stage of the latter. The occurrence of all degrees of this condition in association with a malignant condition of the lung is in accord with this view. Teleky, in 1897, included carcinoma of the lung in his list of causes of "osteopathie hypertrophique pneumique." In a case described by Ash, there was the full picture of chronic hypertrophic osteo-arthropathy with enormous clubbing of the fingers and toes. Additional cases can be found described in the papers of Braun, Brunn, Kornblum, Packard, Young and many others. I found reference to some degree of this condition 13 times in 90 reports of cases selected at random from the more recent literature. Brunn emphasized the importance of careful examination of the pituitary body in all cases of carcinoma of the lung with osteo-arthropathy. Braun actually did find a metastasis in the anterior lobe in such a case, and others have described a general hyperplasia of that lobe in osteo-arthropathy associated with pulmonary carcinoma.

#### MICROSCOPIC PATHOLOGIC ANATOMY

For discussions of the microscopic pathology of carcinoma of the lung, reference may be made to such general articles as those of Barron, Breckwoldt, Briese, Eismayer and Marchesani.

Probably not another regional carcinoma exhibits so wide a range of architecture as the one under consideration. All possible structural and cellular types are found, from scirrhus and diffuse medullary forms through less fully developed acinar and glandular structures to papilliferous cystadenocarcinoma with elaborate dendritic processes extending into the cystic spaces. There is no agreement in statistical studies as to the percentage of each structural type. In general, it may be stated that in the earlier statistics the adenocarcinomatous group was considered to be much the more abundant, while in recent studies the recognition of certain undifferentiated types as carcinoma and not sarcoma has increased the scirrhus and medullary divisions. As a matter of fact, the available material does not lend itself to analysis from this standpoint, since, in reports of cases, glandlike architecture is usually fully



described, while that of the undifferentiated and squamous cell varieties is left to be inferred, particularly as regards the proportion between carcinoma cells and stroma.

Most carcinomas of the lung, as to cell type, can be assigned a place in the following classification: undifferentiated cell carcinoma, squamous cell carcinoma, and cylindric cell carcinoma.

This general grouping differs somewhat from that of Marchesani, which was also used by Breckwoldt. They recognized four types: basal cell carcinoma, polymorphous cell carcinoma, cornifying squamous cell carcinoma and cylindric celled adenocarcinoma.

My modification is made on the grounds that the prototype of the undifferentiated cell usually cannot be made out, that it may have come originally from either a squamous or a gland cell epithelium, and that the conception of cylindric cell mucosae having basal cells has never in this country gained a firm footing.

Satisfactory figures are not available in regard to the incidence of the various cell types. Differences in individual opinion, the existence of intermediate types, and especially the fact that the degree of differentiation may vary in different portions of the same neoplasm have hindered such studies. Barron found the cylindric cell carcinoma the most common; Henrici found but twelve of the squamous cell type among eighty-five collected from the literature. Among fifty-seven selected cases of bronchiogenic carcinoma reported in the literature, I found twenty-five that were stated to be squamous celled; twenty cylindric, cuboidal or gland celled, and ten polymorphous, round or oval celled.

The carcinomas of the lung which may be grouped as of undifferentiated cell type have only of late received a proper interpretation. Formerly they were called sarcomas. Adami appreciated this difficulty and wavered between a diagnosis of carcinoma and one of sarcoma in his case reported in 1895-1896. Von Glahn's eighth case, which he finally styled "alveolar sarcoma or preferably a mesothelioma arising from the pleura," was undoubtedly of this type. It is now known that, apart from lymphosarcoma of the lymphoid apparatus, primary sarcoma of the lung is one of the rarest of blastomas (Ewing). Architecturally, such carcinomas are usually described as carcinoma solidum, or medullary carcinoma, sometimes as scirrhous. They occur at the hilum of the lung in almost all cases and spread extensively in the mediastinum and over the pleura, where they have been erroneously counted as "mesotheliomas." They may be composed of very small cells with scant cytoplasm, inviting confusion with lymphoblastoma, or of large round cells, polyhedral, or even, in part, spindle cells, as Ewing stated.

Carcinoma composed of squamous cells may be either cornifying or noncornifying. The cornifying type presents no difficulty in classification as to cellular structure and therefore ranks high in statistics pre-

pared from reports of single cases. There are many reports of this type throughout the literature (Ernst, Meyer, Moise, Perls, von Glahn and others). The noncornifying type merges, in its less differentiated forms, with certain types characterized by polymorphous and so-called basal cells. It probably goes unrecognized rather often. It occurs much more frequently than the cornifying type.

The type in which cylindric cells prevail is highly variable. In its most completely differentiated form, the cells may be ciliated and borne on a branching papillomatous stroma proceeding into dilated alveolar spaces. The papillomatous structure appears in most instances of carcinoma of the lung of the diffuse type, to which reference has been previously made. Forms made up of lower cylindric and cubical cells occur; likewise, all intermediate forms between a clearcut adenocarcinoma, an acinar structure with solid nests of cells, and a medullary or even scirrhous carcinoma. With the various forms built of cylindric cells the question of the formation of mucin always arises. True epithelial formation of mucin has been demonstrated repeatedly by specific stains. The mucin may be so abundant as to be released in quantity in alveolar spaces, or it may be retained in droplet form within neoplasm cells of "signet-ring" type.

#### HISTOGENESIS

Much of the effort which has gone into the study of carcinoma of the lung has been expended in endeavoring to settle problems of histogenesis. This question, which, alone, would provide material for an extensive general review, can be presented only briefly here. The discussions by Feyrter, Meyer, Eismayer and Marchesani give the more recent views on this subject. Practically every case reporter has reached an opinion in regard to whether the origin of his case should be assigned to the bronchial mucosa, the bronchial mucous glands or the alveolar epithelium. Such decisions have been based on (1) position of the growth in the lung; (2) behavior in respect to various structures of the lung, and (3) cell type, including cell products, such as mucin.

As to position in the lung, it can be asserted that those growths which are grossly of the type associated with the hilum have their origin in bronchial structures, either the mucosa or the mucous glands. It cannot be assumed, on the other hand, that those found well out in the lung are of alveolar epithelial origin. Such tumors may arise from the epithelium of the smaller bronchi or from the cubical epithelium of an attempted regeneration (cells of Tripier), which is bronchiolar rather than alveolar.

As to the manner of growth, particularly in relation to the structures of the lung, it has been assumed that the neoplasms which are diffuse

throughout a lobe or lung, covering the alveolar walls, are the result of direct origin from the alveolar epithelium. Boecker showed that the architecture of the tumor which he described could be explained as a progressive growth from alveolus to alveolus, which utilized the original stroma as the neoplasm spread. Henrici expressed the same opinion in 1912. A polypoid or papillomatous growth into the lumen of a bronchus, or an irregular thickening and roughening of the mucosa, may indicate an origin from the bronchial epithelium, if an extensive infiltration around the bronchus is not present also. A marked peribronchial growth with early stenosis has been thought to imply an origin in the bronchial mucous gland.

On the type of cell of which the neoplasm is composed, alone, in many cases, an opinion has been founded as to the histogenesis of a carcinoma of the lung. In the early literature, a neoplasm made up of squamous cells was often assigned an alveolar epithelial origin with apparently not a reason other than that its cells were flattened. Especially tall columnar cells were considered to indicate an origin from the bronchial epithelium, and a formation of mucin to signify a neoplasm arising in the mucous glands. It is only now beginning to be understood generally that the type of cells of which the carcinoma of the lung is constituted is much more an indication of the degree of differentiation than of the precise histogenesis. As Klotz and others have pointed out, the epitheliums of the bronchi, bronchioles and respiratory alveoli have a common parentage and must be possessed of similar potentialities of differentiation or lack thereof. A broader view of the biologic aspects of the whole question shows how impossible it is to ascertain the origin of carcinoma of the lung by identification of its type of cells, alone. It has repeatedly been pointed out that different parts of the same neoplasm may show entirely different types of cellular organization. There are not only different degrees of anaplasia for different neoplasms, but also variations in the degree of differentiation throughout the life history of a given neoplasm for different areas of its growth.

The relationship of the cornifying squamous cell carcinoma to metaplasia is firmly established. Some writers prefer to follow Goldzieher in considering the change in cell type a "basal cell proliferation with partial differentiation" rather than a true metaplasia. Haythorn, Askanazy and others have shown that such a change in the lower tracheal and bronchial mucosa is of frequent occurrence. Bronchiectatic cavities are especially apt to show it. The frequent origin of carcinoma formed of squamous cells in such cavities thus finds a ready explanation. This type of carcinoma may arise, in a peripheral position in the lung, from small bronchi, bronchioles or possibly alveolar epithelium.

Summing up present day opinion in regard to the histogenesis of carcinoma of the lung, it is clear that most cases are regarded as of bronchial origin, and that proof of the origin of carcinoma of the lung from histologically unaltered alveolar epithelium is lacking. The cyto-architecture reveals the degree of differentiation and not the histogenesis. The formation of mucin does not prove origin from the bronchial mucous glands; but the manner of growth and the character of the bronchial mucosa may serve to differentiate between carcinoma originating in the mucous glands and carcinoma originating in the bronchial mucosa. The histogenesis of the type formed of squamous cells as following metaplasia is fully accepted.

Most carcinomas of the lung are too far advanced when seen to give any sure indication of their origin. As Marchesani suggests, systematic studies postmortem should in time provide examples of early stages of carcinoma of the lung in patients dying of other diseases. Only by such chance opportunities can some of the questions of histogenesis be answered.

#### THE PATHOLOGIST IN THE DIAGNOSIS OF CARCINOMA OF THE LUNG INTRA VITAM

Considerations of the symptomatology, the diagnosis and the treatment of carcinoma of the lung are outside of the limits imposed by the title of this review. A reference must be made, however, to the assistance which the pathologist may render in the diagnosis of the condition intra vitam.

Since carcinoma of the lung is usually carcinoma of the larger bronchi; skillful bronchoscopy becomes, in selected cases, the most useful procedure in making a diagnosis (Killian; Jackson, et al.; McCrae, Funk and Jackson). Not only does the bronchoscopist learn much from the form, color and movement of the bronchi but he frequently finds it practicable to remove a portion of an intrabronchial growth for biopsy. The pathologist may thus have an opportunity to see bronchial carcinoma in a relatively early stage. Benign polypoid growths must be excluded. Examples of malignant growths thus diagnosed after biopsy may be found in reports by Jackson and his associates, Hyde and Holmes, Ephraim and others.

In the second place, biopsy of secondarily involved lymph nodes enables the pathologist to determine the presence of malignancy and also its general type. With the help of a careful physical examination and roentgenoscopy the diagnosis may thus be established.

The sputum resembling currant-jelly or raspberry-jelly described by the earlier writers is rarely seen (Hampeln), although a streaking with blood or even an abundant hemorrhage is common in the later course of the disease. The pathologist may, on rare occasions, make



a diagnosis from fragments of the tumor discovered in the sputum. Betschaert reported the diagnosis of pulmonary carcinoma by this method in 1895 and reviewed the scant literature on the subject, which revealed three previous cases. Pfahler reported a diagnosis similarly obtained in discussing Bryan's paper, and Barker's patient twice coughed up masses of tissue. The second specimen was examined and it led to a diagnosis of squamous cell carcinoma.

Hellendahl reached a diagnosis of "sarcoma" in two instances by a histologic examination of a specimen of tissue obtained by probatory puncture. He quotes Krönig as the only one preceding him in the use of this method for diagnosing carcinoma of the lung. A presumptive diagnosis of carcinoma in the case reported by Perry was made from the tissue found plugging a large trochar which had been deeply inserted into the lung.

The examination of the pleural fluid for cells of the neoplasm has been investigated, particularly by Seecof, who was able to make diagnoses in agreement with the subsequent observations at autopsy in 79 per cent of a series of 38 pleural fluids. The diagnosis from isolated cells is much less certain than that from clumps of cells in normal relation to each other.

Thus it may be seen that the pathologist can have an important part in establishing the diagnosis of carcinoma of the lung during the life of the patient. It is gratifying that statistical studies show that the condition is being diagnosed during the life of the patient much more often than only a few years ago. Brunn found that there are at least 28 examples of surgical intervention in the literature, and he cites cases of Sauerbruch in which the patients were living five years and three years after the operations, respectively.

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## Notes and News

**University News, Promotions, Resignations and Appointments.**—Aurora James Miller, formerly professor of clinical pathology in the University of Nebraska, Omaha, has been appointed professor of pathology and bacteriology in the University of Louisville School of Medicine.

Donald C. Beaver has been appointed first assistant in pathologic anatomy at the Mayo Clinic, Rochester, Minn.

James Henry Dible, professor of pathology and bacteriology in the Welsh National School of Medicine, Cardiff, has been appointed professor of pathology in the University of Liverpool in the place of Warrington York who has been appointed professor of tropical medicine.

James S. Simmons, Major in the Medical Corps of the U. S. Army, formerly in charge of the bacteriologic department of the Army Medical School, Washington, D. C., has been appointed to the army research board in the Bureau of Science, Manila, P. I.

George T. Caldwell, formerly professor of pathology in Baylor Medical College, Dallas, Texas, has been appointed pathologist of the Charles T. Miller Hospital, St. Paul, Minn., and a member of the department of pathology in the University of Minnesota.

William Thalhimier, formerly pathologist to the Columbia Hospital, Milwaukee, has been appointed director of the Nelson Morris Institute for Medical Research and of the laboratories of Michael Reese Hospital, Chicago, in place of Oscar T. Schultz who resigned on account of ill health.

Otto Saphir, senior instructor in pathology in Western Reserve University and pathologist to the Cleveland City Hospital, has been appointed pathologist to Michael Reese Hospital, Chicago.

**Research Award by The American Society of Clinical Pathologists.**—An award will be given annually for work in clinical pathology by a member of this society. The prize will be known as the Ward Burdick Research Award of the American Society of Clinical Pathologists and is to perpetuate the memory of the late Dr. Ward Burdick, who fostered the growth of the society as a founder and as its secretary. The award will be in the form of a gold medal for worthy research in any of the fields of clinical pathology. Candidates for the first award must present the reports of their work at least two months prior to the annual meeting to be held in Portland, Ore., July 5, 6 and 8, 1929. Correspondence should be addressed to the American Society of Clinical Pathologists, Metropolitan Building, Denver.

**Pathologic Fellowships in Charity Hospital, New Orleans.**—The pathologic department of the Charity Hospital, reorganized and placed under the directorship of Dr. Rigney D'Aunoy, offers, beginning July 1, 1929, fellowships in pathology. These fellowships extend over a period of two years, and carry with them the rank of assistant resident pathologist and junior resident pathologist of the Charity Hospital. Full maintenance and a stipend of \$900 and \$1,800 yearly is offered fellows. The laboratories are well organized and equipped and provide material for excellent training in the field of laboratory medicine.

**The Japanese Journal of Experimental Medicine.**—*The Japanese Journal of Experimental Medicine*, edited by Toneji Miyagawa, is a continuation of the Scientific Reports of the Institute for Infectious Diseases of Tokyo Imperial University. The articles are either in the English or in the German language. The first number appears as number 1 of volume 7.

## Abstracts from Current Literature

### Experimental Pathology and Pathologic Physiology

METABOLISM OF TOTAL BASE IN NEPHRITIS. G. L. BOYD, A. M. COURTNEY and I. F. MACLACHLAN, *Am. J. Dis. Child.* **36**:16, 1928.

There is relatively slight variation in the concentration of the total base of the plasma in different types of nephritis. Such cases as show chronic diffuse or interstitial nephritis, renal acidosis associated with increase in blood phosphates and a positive retention of sodium and chlorine in the body when in conjunction with anasarca tend to be accompanied by a decrease in the concentration of the base of the plasma. This decrease is usually to a low normal, or a slightly lower than normal, figure. It was observed that retention of nitrogen or its absence exerted little effect on the level of the base of the plasma. Neither could a constant relationship be demonstrated between the base of the plasma and the blood dilution, or the base retention of the body, other than the sodium retention.

The total base excreted by a nephritic kidney is usually less than normal, provided diuresis is not occurring or that functional impairment is not present owing to the mild character of the lesion.

Nephritic kidneys which are unable to excrete normal amounts of fixed base show an increase in the excretion of total base and its constituent elements in the feces.

The total base excretion, urine and fecal, in patients with nephritis exceeded that in normal children, despite a comparable intake.

H. E. LANDT.

THE INFLUENCE OF SLEEP ON BASAL METABOLISM OF CHILDREN. CHI CHE WANG and R. KERN, *Am. J. Dis. Child.* **36**:83, 1928.

The authors set forth the fact that there is a definite reduction of heat production in sleeping children. Their data were collected from the study of twelve children. They also conclude that Benedict's standards for basal metabolism of children agree more closely with results obtained for young children during sleep than with those for older children.

H. E. LANDT.

FACTORS INFLUENCING THE EXCRETION OF CALCIUM. B. HAMILTON and M. MORIARTY, *Am. J. Dis. Child.* **36**:450, 1928.

The normal variations of the excretion of calcium in the stools of a breast-fed infant were studied; it was found that the excretion of calcium was influenced chiefly by the intake of total fixed base and to a lesser degree by the intake of calcium. As the total fixed base was closely related to the buffer content of the milk (base minus chloride), it seems probable that it was the buffer content of the milk which had this influence on the excretion of calcium in the stools. This view is strengthened by the results in some experiments in which acid and alkali were added to the milk.

The close relationship between calcium in the stools and milk base makes it probable that the former was formed before the latter was absorbed, that is, in the small intestine.

AUTHORS' SUMMARY.

THE RESPIRATORY METABOLISM IN INFANCY AND CHILDHOOD. J. R. WILSON, S. Z. LEVINE and G. GOTTSCHALL, *Am. J. Dis. Child.* **36**:470, 1928.

The author reports a study of the carbohydrate metabolism of normal and marasmic infants. Some of the infants received subcutaneous injections of insulin before the procedure; an equal number did not. It was found that normal infants



may burn about 0.5 Gm. of carbohydrate per kilogram per hour after the ingestion of a large dextrose meal. Marasmic infants burned more than 0.5 Gm. per kilogram per hour. They burn less than 0.5 Gm. per kilogram per hour on the basis of expected weight for age.

The amount of carbohydrate combustion in an infant at rest following the ingestion of a large dextrose meal depends directly on the amount of metabolic protoplasmic tissue in the infant. The previous administration of insulin had no effect on the amount of carbohydrate burned in normal or marasmic infants. Thus, insulin is not indicated as a therapeutic measure in marasmus.

H. E. LANDT.

THE RÔLE OF HEMOLYSIS IN JAUNDICE OF THE NEW-BORN INFANT. J. McKENNEY MITCHELL, *Am. J. Dis. Child.* **36**:486, 1928.

The blood serum of the mother contains a substance capable of hemolyzing the red blood cells of her infant in vitro. This substance is demonstrated in 51 per cent of thirty-three infants with jaundice. It is also demonstrated in lower titer in the cord blood of 22 per cent of thirty-three infants with jaundice. All cord serums show an indirect van den Bergh reaction higher than normal. The direct van den Bergh reaction is not present in cord serums. The serums of all infants under 14 days of age show an indirect van den Bergh reaction higher than normal and higher than that of the cord serums. The reading parallels the intensity of jaundice. The direct reaction is not present in simple icterus neonatorum. Increased fragility of the red blood cells is not a factor in the production of jaundice or in cases showing hemolysis by the mother's serum. The time of formation of the blood group in new-born infants does not bear any relation to jaundice.

H. E. LANDT.

THE FLUCTUATION IN BLOOD SUGAR DURING ECLAMPSIA AND ITS RELATION TO THE CONVULSIONS. P. TITUS, P. DODDS and E. WILLETTTS, *Am. J. Obst. & Gynec.* **15**:303, 1928.

By means of serial readings of the sugar content of the blood, Titus, Dodds and Willetts demonstrated a disturbance in carbohydrate metabolism in eclampsia characterized by a drop in the sugar content of the blood preceding the convulsion. The convulsive seizures occur at levels designated as "absolute," or "relative hypoglycemia," the latter being a sudden definite drop in the sugar content of the blood as compared with previous readings. Following the convulsion there is usually a temporary rise in blood sugar, which is considered the customary response in the liver to muscular activity. There is a tendency to remissions at a lower level so that there is a general trend to a lower sugar content, effecting an eventual exhaustion of the glycogen reserve stored in the liver. The authors conclude that all toxemias of pregnancy are related, and that they are not due to specific toxins of fetal origin. The toxemias are due to a disturbance of maternal metabolism due, primarily, to a deficiency in carbohydrate. The convulsion is comparable to that of hypoglycemia on excessive administration of insulin. The authors therefore propose the injection of dextrose intravenously, 300 cc. of a 25 per cent solution at stated intervals.

A.J. KOBAK.

THE TOXICITY OF BLOOD SERUM PROTEINS IN ECLAMPSIA. A. F. LASH and W. H. WELKER, *Am. J. Obst. & Gynec.* **15**:511, 1928.

Blood was obtained from two patients with eclampsia intrapartum and postpartum. After injecting the blood serum proteins fractionated by the method outlined by Hektoen and Welker, the authors concluded that the blood of patients with eclampsia does not show evidence of toxicity in mice, although injected in large doses intraperitoneally.

A. J. KOBAK.

GESTATION IN A MONKEY (*MACACUS RHESUS*) AND ASSOCIATED PHENOMENA.  
C. G. HARTMAN, *Am. J. Obst. & Gynec.* **15**:534, 1928.

For two years, Hartman studied the menstrual cycle and the various matings of the monkey in the case reported. Each cycle was twenty-eight days and lasted less than five days. The vaginal secretion was removed by the "lavage" method, that is, by washing the vagina with from 2 to 3 cc. of physiologic sodium chloride solution (the amount varied with the size of the animal). The material thus obtained was placed in a graduated centrifugated tube. After the sediment had settled, it was measured, and then this was again mixed and further diluted and methylene blue added for a cellular study. The leukocyte count dropped to nearly zero in the interval of the cycle. The greatest desquamation was reached in the latter part of the interval, and then a fall to an extremely low cell count occurred at the time for menstruation. The animal, after seven matings, became pregnant only when mated on the interval or twelfth day of the cycle with the leukocyte count at that time showing almost no cells. The pregnancy lasted six lunar months. A slight bleeding occurred on the fourteenth and lasted to the thirty-seventh day of gestation. This was presumed to be from the immature placenta, the so-called "placenta sign" of Long and Evans.

A. J. KOBAK.

ERGOT POISONING POSTPARTUM. H. LEO MOSKOVITZ, *Am. J. Obst. & Gynec.* **15**:549, 1928.

From a review of the literature back to 1900 and a study of his own case, Moskovitz shows that ergot poisoning occurs in many cases as an individual idiosyncrasy.

A. J. KOBAK.

THE EFFECTS OF LIGATION OF PANCREATIC DUCTS ON GASTRIC DIGESTION.  
S. A. YESKO, *Am. J. Physiol.* **86**:483, 1928.

In dogs, the effect of ligation of pancreatic ducts showed that with complete absence of pancreatic secretion there was only a slight rise of gastric acidity; the stomach emptied faster; there was increased gastric protein digestion, and increase of blood amylase. Good health was maintained, but there was progressive loss of weight.

H. E. EGGERS.

THE EFFECT OF SUPRARENAL INSUFFICIENCY ON REPRODUCTION AND THE OESTROUS CYCLE IN THE ALBINO RAT. L. C. WYMAN, *Am. J. Physiol.* **86**:528, 1928.

Double suprarenalectomy in the white rat was found to result in complete or partial inhibition of estrum, the degree of disturbance of ovarian function being correlated with the severity of the insufficiency. The relation appeared to be indirect, working through intermediate factors which were probably metabolic.

H. E. EGGERS.

THE VALUE OF ACTEROL (IRRADIATED CHOLESTEROL) IN THE TREATMENT OF THYROPARATHYROIDECTOMIZED DOGS. J. C. BROUGHER, *Am. J. Physiol.* **86**:538, 1928.

The onset of a violent attack of tetany is prevented in parathyroidectomized dogs by the administration of 0.4 cc. of irradiated cholesterol in the presence of milk. Absence of the latter as a source of calcium renders the irradiated cholesterol without effect. Irradiated cholesterol induces more rapid recovery time than does cod liver oil: from fifteen to thirty days for the former, and from thirty to forty days for the latter. Apparently, a large supply of vitamin D is effective in many instances to enable the body to use calcium in the condition of parathyroid tetany.

H. E. EGGERS.

LEUKOCYTE CHANGES AFTER ADRENAL REMOVAL. R. L. ZWEMER and C. LYONS, *Am. J. Physiol.* **86**:545, 1928.

In cats which survived adrenalectomy for a long time there was observed a decrease in the number of polymorphonuclear neutrophils and an increase in the small mononuclears. This may be preceded by a postoperative rise in the number of all the white cells associated with trauma and healing. Animals which failed to survive the necessary period showed high total and neutrophil counts—the typical picture of infection. The total count was found to be increased by cold, without effect on the differential count. This increase was apparently related to reaction by the sympathetic nervous system.

H. E. EGGERS.

THE EFFECT OF WITHDRAWAL OF DRINKING WATER ON THE SUSCEPTIBILITY OF RATS TO CERTAIN DRUGS. G. CRISLER, *Am. J. Physiol.* **86**:552, 1928.

When rats were withheld from drinking water for forty-eight hours or more, they showed increased susceptibility to morphia and to magnesium sulphate, and diminished susceptibility to strychnine. It is suggested that in the depression stage of dehydration, animals are more susceptible to depressant drugs, and less sensitive to those which kill by stimulation.

H. E. EGGERS.

A HORMONE MECHANISM FOR GALL-BLADDER CONTRACTION AND EVACUATION. A. C. IVY and E. OLDBERG, *Am. J. Physiol.* **86**:599, 1928.

Intravenous injection of an extract of upper duodenal mucosa was found to cause contraction and evacuation of the gallbladder. This extract was free from vasodilatin and was without objective toxic effect on unanesthetized dogs. Since cross-circulation experiments showed that the injection of acid into the duodenum caused the appearance of a substance in the blood which resulted in contraction of the gallbladder, the mechanism would appear to be that of hormone action, and for this hormone and the active substance of the intestinal extract, the writers propose the name "cholecystokinin." In addition to dilute acids, the following substances caused contraction of the gallbladder after injection into the duodenum: butter, digested egg yolk, cream and olive oil, and 5 per cent soap solution. Undigested egg yolk, cream or olive oil were without effect. Spontaneous rhythmic contractions of the gallbladder which were observed were increased in amplitude by small doses of "cholecystokinin"; larger doses caused their disappearance during the height of the induced contraction, but they reappeared during the subsequent relaxation. If they were not present prior to the injection, they would frequently appear during the late stages of relaxation. During the contraction, the hepatic ducts were observed to be injected with iodized oil 40 per cent, owing, it was believed, to increased tone of the duodenum or of the sphincter of Oddi.

H. E. EGGERS.

CHANGES IN BLOOD SUGAR FOLLOWING INJECTIONS OF PEPTONE IN THE DOG. W. W. BRANDES and J. P. SIMONDS, *Am. J. Physiol.* **86**:618, 1928.

In anesthetized dogs, the injection of peptone was found to cause a peripheral hypoglycemia during the period of low blood pressure, when the liver is engorged and tense. With rise of pressure and decrease in the tenseness of the liver, there is a marked rise in blood sugar. During the period of greatest engorgement of the liver, a marked rise is noted in the sugar of the blood of the hepatic vein, while at the same time that of the peripheral vessels is low. The writers explain this by the obstruction to the free flow of blood through the liver during peptone shock, with the congestion and local stasis causing increased glycogenolysis. This increased production of sugar is retained locally, owing to the small amount of blood leaving the liver. With relaxation of the circulatory obstruction, the peripheral hypoglycemia gives place to a hyperglycemia when the sugar-laden blood leaves the liver.

H. E. EGGERS.

CHANGES IN THE BLOOD RESULTING FROM MECHANICAL OBSTRUCTION OF THE HEPATIC VEINS. J. P. SIMONDS and W. W. BRANDES, *Am. J. Physiol.* **86**:623, 1928.

After mechanical constriction of the hepatic vein in dogs, the following blood changes were observed: a precipitate fall of blood pressure of from 40 to 60 mm. of mercury, with a fairly constant maintenance at this level during the period of constriction of twenty minutes or more; a decided decrease in blood concentration, averaging 11 per cent in six dogs, with a gradual return to normal during the course of about fifteen minutes; a marked decrease of coagulation time during constriction, followed by an increase on release, and a rapid fall of the blood sugar—to an average of 42 per cent in six dogs—with a rapid rise on release.

H. E. EGGERS.

RICKETS AND TETANY IN RATS. A. T. SHOHL and F. C. BING, *Am. J. Physiol.* **86**:633, 1928.

While correction of the defective mineral metabolism of rickets in rats could be accomplished by two essentially opposed methods—by the use of cod liver oil or irradiated food on the one hand, and by the addition of phosphates to the diet on the other—the animals to which the phosphates were administered showed a temporary hyperirritability of the neuromuscular system which was lacking in the others.

H. E. EGGERS.

ACTIVITY STUDIES ON CASTRATED MALE AND FEMALE RATS WITH TESTICULAR GRAFTS, IN CORRELATION WITH HISTOLOGICAL STUDIES OF THE GRAFTS. C. P. RICHTER and G. B. WISLOCKI, *Am. J. Physiol.* **86**:651, 1928.

The activity of castrated rats, which is much less than that of normal animals, was found to be greatly increased by testicular grafting, being in general proportional to the state of preservation of the graft. In none was the testicular tissue absolutely normal, but the "takes" were much better in the male than in the female animals. The increase of activity was much less than that resulting from ovarian transplantation.

H. E. EGGERS.

THE BASAL METABOLISM DURING THE OESTROUS CYCLE IN THE RAT. M. O. LEE, *Am. J. Physiol.* **86**:694, 1928.

From a total of 282 basal metabolism determinations made on nine female rats during all stages of the estrual cycle, it was found that in all the animals there was increased heat production during the last ten hours of the diestrus stage, and in the first six hours of the proestrus. No change in metabolic rate was found at any other stage. The increased heat production during the end of the diestrus is comparable to the slight increase reported in menstruating women. No constant changes were found in the respiratory quotients determined in two rats during all stages of the cycle.

H. E. EGGERS.

THE CONSTITUTIONAL ENTITY OF EXOPHTHALMIC GOITER AND SO-CALLED TOXIC ADENOMA. A. S. WARTHIN, *Ann. Int. Med.* **2**:553, 1928.

(On February 19, 1924, Warthin addressed a joint meeting of the St. Louis Medical Society and the American College of Physicians on the subject which forms the title of this paper. Even though the address was not published until December, 1928, the literature of the past five years has contained several references to Graves' constitution (Warthin), for the most part in communications published by those who had learned of this constitutional entity through association with Warthin.)



An apparently constantly enlarging clinical syndrome, referable to the thyroid gland, is embraced under the general conception of hyperthyroidism and variously designated as toxic goiter, toxic thyroid and toxic adenoma. Clinicians have endeavored to distinguish this form of disease of the thyroid gland from typical or true exophthalmic goiter. Warthin has attempted to correlate the various clinical conceptions of these diseases with the pathologic histology of the thyroid gland. The abundance of material which has poured into pathologic laboratories during recent years should aid in clarifying the divergent views on the pathology of the thyroid gland.

To the original triad of goiter, tachycardia and exophthalmos, recognized vaguely by Parry (1825) and more accurately by Graves (1835) and von Basedow (1840), has been added symptom after symptom until, at the present time, it has become practically impossible, in many cases, to distinguish between what some authors regard as exophthalmic goiter and what others call by such names as toxic adenoma and toxic goiter.

The present day conception of exophthalmic goiter is that of an extremely variable and broad syndrome. Considered analytically, this syndrome presents a clinical picture of a well defined type of person, a distinct pathologic constitution. American writers on goiter have not grasped this fact, but in Germany and Italy, various investigators are beginning to speak of the hyperthyroid constitution. Warthin prefers to term it Graves' constitution in the absence of any positive proof that thyroid hypersecretion is the underlying etiologic factor.

The person with the Graves constitution usually has a youthful build with a slender skeleton, and is usually underweight. The facies has a bright-eyed, quick-reactioned appearance. Tremor of the muscles is usually present. The skin is warm, moist, delicate and translucent, often with a tendency to excessive pigmentation when exposed to light. Vitiligo is not rare. Hyperhidrosis and dermatographia are common. The neck is usually rounded and full; the cervical lymph nodes are enlarged. The thyroid gland is usually, though not always, enlarged. All conditions of the eyes exist, from the vivacious, widely opened state to frank exophthalmos. There is marked cardiac excitability, usually with tachycardia. The pulse is rapid and full and frequently irregular. Vasomotor instability, with flushing, sweating and circumscribed edemas is commonly seen. Instability of the central nervous system manifests itself in increased sensibilities and emotional responses, quickness of perception and reaction, unrest and haste, anxiety, insomnia, flights of ideas and even hysteria and psychosis. Usually, however, the mental powers are well developed and remain well preserved. The marked irritability of the sympathetic nervous system is a predominant characteristic of the condition. The basal metabolism is definitely elevated. The appetite is abnormal; but despite overeating, the person remains thin or loses weight. There is frequently a lowered tolerance for carbohydrates with the development of hyperglycemia. Allergic reactions are common. A mild anemia usually exists, with a relative lymphocytosis. Psychical frequently exceeds physical sexual excitability. Impotency is common in the male, menstrual disturbance in the female. There is diminished tolerance for thyroid preparations, iodine and epinephrine. The most striking features of Graves' constitution are expressed in juvenile morphology and rapid functional reactions. Obviously, these constitutional features will appear in varying degrees of intensity and in varying combinations in different persons.

The clinical diagnosis of hyperthyroidism is frequently being made from the presence of one or two of the symptoms which may belong to the constitutional picture just described, but which may not be associated with any disturbance of thyroid function. Many normal thyroid glands, simple goiters and adenomas are called hyperfunctioning or toxic and are ligated and resected, only to show that histologic examination does not confirm the clinical diagnosis.

Numerous instances of iodism are resulting from the widespread use of preparations of iodine. Symptoms of palpitation, excitable pulse and nervousness appear; resection is ultimately performed, and the pathologist finds nothing but thin, watery colloid and follicular atrophy; he can do no more than return a diagnosis of "hyperiodism."

If the pathologist accepts the histologic criteria used commonly for the diagnosis of hyperthyroidism or toxic adenoma, namely, epithelial hypertrophy and hyperplasia, he falls at once into difficulties, for many of the thyroid glands sent to him will present no such evidence. If the classic clinical signs of exophthalmic goiter are present, the pathologist expects to find diffuse parenchymatous hyperplasia and metaplasia with total absence, or marked decrease, of colloid. When these are found, the pathologist unhesitatingly makes a diagnosis of exophthalmic goiter. If the parenchymatous hyperplasia is focal, many pathologists will regard it as evidence of early, moderate or incomplete exophthalmic goiter. The greatest difficulty presents itself in those cases in which, with precisely the same symptomatology, no epithelial hyperplasia or hypertrophy can be found. The pathologist is further perplexed by the fact that epithelial hypertrophy may be found in the thyroid glands of persons who were not suspected clinically of thyroid hyperfunction or dysfunction. There is no positive knowledge as to the exact relationship between the histologic appearances of the thyroid epithelium and its functional activity. As far as thyroid epithelium is concerned, therefore, there are no histologic criteria that give a pathologic unity to all the clinical forms of thyroid hyperfunction or dysfunction.

Warthin considers that the most interesting and striking feature of the thyroid gland in exophthalmic goiter is the constant presence of hyperplastic lymph nodules with large germinal centers showing the characteristic lymphoid exhaustion of the thymicolymphatic constitution. American authors have attached no significance to this constant observation. On the other hand, a large number of European authors have noted the constant presence of an enlarged thymus in cases of exophthalmic goiter. A few mention the presence of hyperplastic lymph nodes within the thyroid itself. Chvostek, however, is almost the only author who regarded the general picture of exophthalmic goiter as indicating the thymicolymphatic constitution. No one has observed the occurrence of the same pathologic constitution in the so-called toxic adenoma.

Warthin's experience has been vastly different. In the first sections of exophthalmic goiter which he studied, he was struck by the presence of hyperplastic lymphoid tissue with exhaustion of the germ centers, resembling that of the thymicolymphatic constitution. Warthin recently restudied 976 resected thyroid glands submitted to him from 1900 to 1923, the autopsy material of thirty post-operative deaths in cases of exophthalmic goiter and in five deaths in acute cases of this disease without operation, and the thyroid glands at 1,000 autopsies in which the thyroid had been examined by the routine procedure. In 150 of the autopsies, a pathologic diagnosis of thymicolymphatic constitution had been made.

Among the 976 resected thyroid glands were 50 which showed diffuse epithelial hypertrophy and hyperplasia with lymphoid hyperplasia; 45 showed nodular colloid goiter with focal epithelial hypertrophy and lymphoid hyperplasia; 58 were true adenomatous colloid goiters with focal epithelial hypertrophy and lymphoid hyperplasia; 92 were true adenomatous colloid goiters with lymph hyperplasia, but without epithelial hypertrophy.

The clinical diagnosis of exophthalmic goiter, hyperthyroidism, toxic goiter or toxic adenoma was made in the case of adenomatous, nodular and colloid goiters showing lymphoid hyperplasia, either with or without epithelial hypertrophy. As far as could be learned, other signs of Graves' (thymicolymphatic) constitution were present in the majority of these cases.

In the 1,000 autopsies studied, 94 cases showed lymphoid hyperplasia of the thyroid gland. In all these cases, as well as in the thirty-five autopsy cases of exophthalmic goiter, with diffuse epithelial and lymphoid hyperplasia, there was found associated the general picture of thymicolymphatic constitution: hyperplastic or persistent thymus, general enlargement of the lymph nodes and spleen, hypoplasia of the suprarenal glands, heart and aorta with other morphologic stigmas.

Warthin states that it is apparent from these studies that the constitutional defect of the thymicolymphatic (Graves') constitution underlies every case of exophthalmic goiter and so-called toxic adenoma. An adenoma of the thyroid

gland, aside from its size and mechanical effects, is clinically important as far as so-called toxic symptoms are concerned only when it is associated with the thymico-lymphatic constitution. Exophthalmic goiter and "toxic adenoma," therefore, possess the same pathologic constitutional entity. Not all cases of thymico-lymphatic constitution will present the Graves syndrome, but all cases with the latter will possess the essential morphologic stigmas of this constitution. Exophthalmic goiter and toxic adenoma are pathologic reactions potentially predetermined in the person at birth by virtue of his constitutional anomaly. Only those possessing this constitutional anomaly will develop so-called hyperthyroid or thyreotoxic symptoms. The potentiality, however, may remain latent or quiescent during all or a large part of the life of a person possessing the constitutional background.

WALTER M. SIMPSON.

ENDEMIC GOITER IN RABBITS. ALAN M. CHESNEY, THOMAS A. CLAWSON and BRUCE WEBSTER, *Bull. Johns Hopkins Hosp.* **43**:261, 278 and 291, 1928.

Marked spontaneous enlargement of the thyroid gland was observed in a series of rabbits kept under identical conditions in the laboratory. The average weight of the thyroid was 2.93 Gm.; the maximum was 43 Gm. The glands showed increased vascularity, with hyperplasia, but without increase in colloid. Enlargement of the suprarenal glands was also present in some of these animals. The time during which the rabbits remained in the laboratory seemed to be a factor in the development of the goiters. Although most of them were used in the study of syphilis, it was possible to exclude this disease as an essential factor in the condition.

The heat production of normal rabbits and those with goiter was studied by means of Marine's modification of Haldane's apparatus for measuring the respiratory exchange in rabbits. In normal animals, the average metabolic rate was 2.64 calories per kilogram per hour, while in those with palpable goiters it was 2.2 calories, a decrease of 16.6 per cent. The decrease paralleled, to some extent, the degree of enlargement of the thyroid. Study of individual animals showed gradual depression of the metabolic rate, with growth of the goiter in the majority. Certain animals, which died without obvious cause but with extreme loss of weight, showed an average increase of 20 per cent in their metabolic rate before death.

Administration of iodine in the form of a compound solution of iodine, 0.06 cc. daily, caused a temporary lowering of the metabolic rate in six normal rabbits, followed by a gradual return to normal. Diffuse out-pouring of colloid was produced, with flattening of the alveolar epithelium, and preponderance of the colloid cells. In rabbits with goiter, on the other hand, there was an immediate increase in the activity of the animals, a marked increase in the metabolic rate, rapid emaciation and death, in most instances. The average increase was 98 per cent, the severity of the reaction being proportional to the degree of hyperplasia in the gland. Examination of the thyroid glands revealed involution of the hyperplastic glands and lowering of the alveolar epithelium, with areas resembling colloid adenomas. It would appear that, as soon as the deficiency of iodine was supplied, the gland was able to pour an excess of thyroid secretion into the blood. These experiments suggest that large doses of iodine may be dangerous to persons with simple goiters of the iodine deficiency type.

B. R. LOVETT.

ON THE PATHOGENESIS OF THE ARGYLL-ROBERTSON PHENOMENON. SVEN INGVAR, *Bull. Johns Hopkins Hosp.* **43**:363, 1928.

For the evolutionary reasons developed in the article, one must look for the pupillomotor pathways on the surface of the diencephalon. It is known that they take a surface route from the posterior part of the optic tract to the anterior commissure in front of the anterior quadrigeminal bodies. As the metasymphilitic and syphilitic meningitic processes produce successively developing marginal degenerations of the optic pathways, as also of the diencephalic parts on the whole, the pupillomotor pathways must be injured at an early stage. In fact, all the char-

acteristic features of the Argyll-Robertson pupil are to be explained in this manner. The reflex immobility of the pupil is to be considered simply as a meningeitic symptom. In this way only does the Argyll-Robertson pupil acquire significance clinically. The disturbed pupillary reaction to light reflects the processes within the basal subarachnoid spaces along the optic pathways. It appears to be a sensitive indicator of these processes when the disturbance occurs in the early stages. Such an indicator is certainly also the isolated ptosis in metasyphilitic processes. In the same way, one attains an understanding of the pupillary disturbances after traumatic lesions. As all the evidence indicates that only such morbid processes as manifest themselves in producing marginal destructions within the basal subarachnoid spaces of the brain are able to cause the Argyll-Robertson pupil, it is understood that the metasyphilitic and syphilitic diseases hold a monopoly among the causes of this valuable clinical symptom.

## AUTHOR'S SUMMARY.

THE EFFECT OF SODIUM CHLORIDES ON THE CHEMICAL CHANGES IN THE BLOOD OF THE DOG AFTER OBSTRUCTION OF THE CARDIAC END OF THE STOMACH. RUSSELL L. HADEN and THOMAS G. ORR, *J. Exper. Med.* **48**:627, 1928.

A study is reported of the effect of different methods of treatment on the toxemia of cardiac obstruction. The average duration of life of untreated dogs is three days. Three dogs treated with 1 per cent salt solution subcutaneously lived thirty-two, thirty-six and forty-five days, respectively, without developing a toxemia. Two per cent dextrose, similarly given, does not alter the course of the toxemia. Concentrated salt solution in small quantities, given directly into the jejunum, prevents the marked rise in nonprotein nitrogen but does not materially prolong life. Release of the obstruction does not change the course of the toxemia in untreated animals. The subcutaneous injection of 1 per cent sodium chloride solution after release of the obstruction causes a rapid return of the blood to normal and allows the animal to recover. A similar amount of fluid given as 2 per cent dextrose does not alter the course of the toxemia after release of the obstruction.

## AUTHORS' SUMMARY.

THE BLOOD CHLORIDES IN PROTEOSE INTOXICATION. RUSSELL L. HADEN and THOMAS G. ORR, *J. Exper. Med.* **48**:639, 1928.

Dogs injected with proteose recovered from the intestinal contents of animals with obstruction at different levels show no significant changes in the blood chlorides even with a fatal intoxication. After the intravenous injection of lethal and sublethal doses of Witte's peptone, there is little change in the chlorides. Autolyzing liver in the abdominal cavity produces no change in the blood chlorides, even with a great increase in the urea and nonprotein nitrogen. Proteose intoxication is probably not a factor in the characteristic fall in chlorides seen after intestinal and pyloric obstruction.

## AUTHORS' SUMMARY.

ON THE PERIOD OF HUMAN GESTATION. W. A. JOLLY, *J. Obst. & Gynec. Brit. Emp.* **35**:258, 1928.

Two factors determine the length of gestation; they are dependent on the rhythmic endocrine influence, and the irritability and tolerance of the uterus to its distention in the last months of pregnancy. The period of human gestation is related to the length of the menstrual cycle. The physiologic period extends over eleven cycles instead of the current accepted ten cyclic periods. This is reckoned from the middle day of the last cycle, i. e., when the menstrual cycles are short and regular, such as twenty-four days, the pregnancy, counted from the last menstrual flow, lasts 264 days, or eleven cycles. When the period of gestation is figured from the time of ovulation, which is usually about the fourteenth day, the length of gestation would amount to 252 days, or ten and one-half cycles.

A. J. KOBAK.



THE RESORPTION OF THE BILIARY ACIDS IN THE NORMAL AND INFLAMED GALL BLADDER. F. ROSENTHAL and H. LICHT, *Klin. Wchnschr.* 7:1952, 1928.

Severe inflammations of the gallbladder markedly increase the absorption of biliary acids.

E. F. HIRSCH.

HYPOGLYCEMIA IN ADDISON'S DISEASE. W. WADI, *Klin. Wchnschr.* 7:2107, 1928.

The report stresses the hypoglycemia which appeared in the late stages of the disease in his patient, with coma and muscle twitchings. Dextrose temporarily relieved these symptoms.

E. F. HIRSCH.

THE EFFECT OF TRAINING ON THE WORK CURVE OF BLOOD SUGAR. A. HOFMANN, *Klin. Wchnschr.* 7:2043, 1928.

As Bürger already supposed, the hyperglycemia with work diminishes with training, and finally disappears. Further, the hypoglycemia decreases so that finally, in a well trained person, the sugar curve is practically a straight line.

AUTHOR'S SUMMARY.

LIPIN METABOLISM IN FASTING ANIMALS. H. WENDT, *Klin. Wchnschr.* 7:2183, 1928.

In fasting dogs, the phospholipins and cholesterol increase in amount in the peripheral blood during the first few days and gradually decrease later to subnormal values. The free cholesterol and the esterified cholesterol participate about equally in the initial increase and subsequent diminution. The increase of phospholipin and cholesterol ester noted in normal animals after triolein feeding is much more accentuated in the fasting dog. Correlation is sought by the assumption that fat is destroyed more quickly than lecithin or the cholesterol esters.

AUTHOR'S SUMMARY.

### Pathologic Anatomy

MYOCARDITIS. B. J. CLAWSON, *Am. Heart J.* 4:1 (Oct.) 1928.

Myocarditis, acute or chronic, arranged diffusely or in localized areas as Aschoff nodules or abscesses, is a common condition in the myocardium in acute and recurrent rheumatic endocarditis, in subacute bacterial endocarditis and in old valve defects. The periarterial scars appear to be the result of a previous bacterial infection and are frequently found in the myocardium in cases of subacute bacterial endocarditis and old valve defects. Proliferative or exudative inflammation is rare in the myocardium in cases of syphilitic aortitis. Scars resulting from atrophy of muscle with replacement by connective tissue following a narrowing of coronary arteries seldom occur except in the myocardium in cases of hypertension and coronary sclerosis. The extent of myocardial injury as shown by anatomic changes rarely appears to be sufficient to bring about cardiac failure. The conditions usually diagnosed acute or chronic myocarditis cannot be demonstrated clinically to be inflammatory processes and in most cases anatomic injuries are not seen. So-called myocarditis is usually a condition of the myocardium, probably fatigue, which is not manifested anatomically.

AUTHOR'S SUMMARY.

ABNORMALLY LONG PAPILLARY MUSCLES OF THE HUMAN HEART. WALLACE M. YATER, *Am. Heart J.* 4:72 (Oct.) 1928.

This type of anomaly is undoubtedly congenital. Early in the development of the atrioventricular valves, muscular tissue from the myocardium invades the endocardial tissue of the cusps and replaces it. The muscular tissue of the cusps

becomes closely blended with the subjacent musculature of the walls of the ventricles. This stage in the development of the cusps is soon followed by replacement of the muscular tissue by collagenous connective tissue, the process evidently taking place mainly from above downward. The subjacent trabeculate musculature also is replaced by collagenous connective tissue. The fibrous cords so developed are the chordae tendineae. Muscular tissue persists at the parietal ends of the cords and forms the papillary muscles.

In cases such as those just described, the replacement by collagenous connective tissue ceases too soon and is imperfect; muscular tissue is left in place of chordae tendineae. The only other explanation would be that localized endocarditis had produced thickening and retraction of the chordae tendineae, causing the cusp of the valve and the papillary muscle to be drawn together. All the facts, however, are opposed to this conception and point rather to the developmental origin of the condition. The instances of this anomaly previously reported and those described in this paper have not appeared to possess any clinical significance. In case 2 of this series it seemed that the condition might have increased the insufficiency of a dilated mitral ring had such been present, but the mitral orifice was apparently not very incompetent.

AUTHOR'S SUMMARY.

THE RELATION OF THE WEIGHT OF THE HEART TO THE WEIGHT OF THE BODY AND OF THE WEIGHT OF THE HEART TO AGE. HARRY L. SMITH, *Am. Heart J.* 4:79, 1928.

The average weight of the adult male heart is 294 Gm.; that of the adult female heart is 250 Gm. There is a definite correlation between the weight of the heart and weight of the body. The ratio is 0.43 per cent for males, and 0.40 per cent for females; it is slightly higher in thin persons and lower in obese persons. This coefficient is not accurate for body weights of less than 45 Kg. and more than 94.5 Kg. The weight of the heart may be calculated from the weight of the body, with an error varying from 8 to 10 per cent. The weight of the heart does not increase with age, irrespective of the weight of the body; it increases, however, with increase in the weight of the body.

AUTHOR'S SUMMARY.

THE LONGITUDINAL SMOOTH MUSCLE OF THE CENTRAL VEIN OF THE SUPRARENAL GLAND. EARL FLETCHER HENDERSON, *Anat. Rec.* 36:69 (July) 1927.

The musculature of the medullary veins of the suprarenal gland occurs as heavy longitudinal bundles in the wall of the central vein and its tributaries. No circular bundles are found. In smaller veins the bundles are usually single and rounded, and often appear to project far into the lumen of the vessel. In larger veins there are two or more bundles in the wall. Increasing in size and number, they encroach on one another, lose their rounded contour and become more flattened and more uniformly distributed. Before emerging from the gland, the main trunk of the central vein is a thick-walled vessel consisting of an endothelial intima, a strong muscular coat of longitudinal smooth muscle fibers arranged uniformly about its circumference, and a connective-tissue adventitia.

To determine the course of these bundles, segments of the central vein were reconstructed in wax. As small veins with only one longitudinal muscle bundle unite, muscles on adjacent sides of the vessels fuse in the angle of anastomosis. When a larger vein approaches a point of anastomosis with a similar one, the longitudinal fibers usually arrange themselves in two main masses, one on the side nearest the approaching vessel, the other on the opposite side. When the vessels unite, bundles on adjacent sides fuse in the angle; those on opposite sides continue along the outer walls of the vessels.

Because of this arrangement, contraction of the musculature results in dilatation of the central vein. Apparently this muscle regulates the outflow of blood and epinephrine through the suprarenal vein into the general circulation.

AUTHOR'S SUMMARY.

THE SIGNIFICANCE OF THE CONCENTRIC CORPUSCLES OF HASSALL. HARVEY ERNEST JORDAN and GUY WINSTON HORSLEY, *Anat. Rec.* **35**:279 (June) 1927.

Histologic evidence is presented for an interpretation of the concentric corpuscles of the thymus in terms of foci of occlusion of capillaries and precapillary arterioles following endothelial-cell hypertrophy in involution. Structures closely resembling Hassall's corpuscles of the thymus, and clearly representing segments of precapillary arterioles in which the lumen has become obliterated through hypertrophy of the endothelium, are described in the case of certain involuting lymph nodes of the rabbit.

AUTHORS' SUMMARY.

AIR IN THE CORONARY ARTERIES. GEORGE J. RUKSTINAT and E. R. LE COUNT, *J. A. M. A.* **91**:1776 (Dec. 8) 1928.

Experience with some forms of death of human beings and with occurrences in which the approach of death has been close, and the results of experimental air embolism of the pulmonary veins and systemic arteries in guinea-pigs indicate that postmortem examinations of human bodies should now and then be done under water or with other appropriate measures for demonstrating the presence or absence of air in the systemic arteries, especially in those which supply the heart muscle.

In conditions in which air embolism is possible, particularly embolism of the pulmonary veins, the patient should be promptly examined for peculiar churning murmurs of the heart whenever unexpected syncope is encountered and such examinations are feasible.

AUTHORS' SUMMARY.

MUSSEL POISONING. K. F. MEYER, H. HOMER and P. SCHOENHOLZ, *J. Prev. Med.* **2**:365, 1928.

In a review of several phases of mussel poisoning in California in 1927, four fatal cases are reported. The only lesions found were small hemorrhages in the fundus of the stomach and the first portion of the duodenum.

ADDISON'S DISEASE WITH ATROPHY OF SUPRARENAL CORTEX. O. BRENNER, *Quart. J. Med.* **22**:121 (Oct.) 1928.

Five cases of Addison's disease are described. In four of them there was a peculiar and characteristic lesion of the cortex, with destruction of most of it. The medulla was little or not at all injured. In the fifth case no suprarenal glands were found. It is suggested that this may represent the end stage of the process illustrated by the other four cases. It is suggested that the process is a necrosis of cortical cells caused by some unknown toxin which has a special affinity for them. This is followed by focal regeneration, with the production of hyperplastic islands of hypertrophied cells, which are then attacked by the same process. The few cortical cells left after the primary injury are probably overworked, possibly causing part of the subsequent degeneration. In many cases of Addison's disease due to suprarenal atrophy or tuberculosis, other endocrine glands are also diseased. In one case the lesion of the thyroid was almost as marked as that of the suprarenal glands, though there were no symptoms of disease of the thyroid. In another case there were mild symptomless lesions of the thyroid and testis. In another case there were symptoms and pathologic changes of exophthalmic goiter as well as of Addison's disease. In the other two cases the other endocrine glands were not examined. The pathologic evidence as to the relative importance of the cortex and medulla is reviewed. It is shown that the symptoms of Addison's disease occur only when most of the cortex is destroyed, and that they occur then even if the medulla and the chromaffin system are normal. On the other hand, the chromaffin system may be absent, and if the cortex is normal there are no symptoms of Addison's disease. The inference is drawn that the symptoms are due to disease of the suprarenal cortex and not to disease of the medulla or of the chromaffin system as a whole.

CONGENITAL STRUCTURAL ANOMALIES OF THE PULMONARY ARTERY. A. COSTA,  
Arch. di pat. et clin. med. 7:329 (Sept.) 1928.

This study is based on histologic and micrometric examinations of pulmonary arteries (210 cases) in various decades of life and of both sexes. In each instance, the micrometric measurements of the single layers of the arterial wall and the histo-analysis were made in the lower third of the artery. Under normal conditions, the thickness of the media in children varies between 0.35 and 0.5 mm.; in the adolescent periods of life it reaches a thickness of from 0.6 to 0.650 mm., and in advancing age it measures between 0.7 and 0.85 mm. While the intimal layer is extremely thin (0.01 mm.) in the first years of life, it presents in adolescence a gradual enlargement, showing a thickness of from 0.015 to 0.02 mm. and in later decades, 0.03 mm. This progressive enlargement of the media is due to an increase in the density of the circulatory distributed elastic lamellae and to a further development of the muscle tissue. The gradual thickening of the intima occurs on account of the increasing density of the internal elastic membrane and the formation of a delicate subendothelial layer of connective tissue.

The structural malformations found were mainly of hypoplastic nature. Three definite types were observed: 1. Muscular hypoplasia affects the artery diffusely and is characterized by muscle tissue that is little developed or totally absent. The elastic apparatus, as well as the interstitial connective tissues, often appear hyperplastic. However, the muscular hypoplasia rarely occurs, without a concomitant hyperplasia of these two tissues. 2. In another type of musculo-elastic hypoplasia, not only are the muscular elements scarce, but also the structurally important, circularly-running elastic lamellae are extraordinarily thin. The interstitial connective tissue usually exhibits a diffuse hyperplasia. 3. The elastic hypoplasia is characterized by greatly hypoplastic elastic apparatus, while the muscular tissue reaches an otherwise moderate development. In hypoplastic conditions of the first and second types, the media may show a nearly normal thickness (0.75 mm. in persons from 30 to 40 years of age) due to hyperplastic processes of other tissues. In the second type, however, the media never achieves its normal size and the pulmonary artery then greatly resembles its early (from 1 to 5 years of age) forms during extrauterine development. The intima does not exhibit any structural abnormalities in the aforementioned hypoplastic conditions of the media, except that the internal elastic membrane participates, more or less, in hyperplastic or hypoplastic processes of the media layer. These investigations do not confirm the observations of Orliansky in regard to hypoplasia of the cerebral arteries (Thèse de Genève, 1919).

In 14 per cent of all the cases examined post mortem, such structural anomalies of the pulmonary artery were observed. One could not establish any correlation between the described anomalies of the pulmonary wall and the development of atherosclerosis. In 90 per cent of the cases investigated there was a parallelism between the hypoplasia of the aorta and hypoplastic conditions of the pulmonary artery; in 16 per cent of the cases with the latter condition a chronic pulmonary tuberculosis was present.

E. L. MILOSLAVICH.

THE THYROID GLAND IN GOITROUS AND GOITER-FREE REGIONS. H. MAY,  
Arch. f. klin. Chir. 149:501, 1928.

May studied the size of the acini and the extension of epithelial proliferation in nongoitrous thyroid glands from different regions. He found a larger histologic development of the thyroid glands of the goitrous region compared with the glands of goiter-free regions. This difference appears striking in a comparison of the enlargement of the thyroid glands at puberty. In the female the histologic development at puberty is always more extensive than in the male. The thyroid gland of the male becomes noticeably enlarged after the age of 60, a new proliferation which does not seem to occur in the female.

C. A. HELLWIG.



TOLUYLENDIAMINICTERUS. H. EITEL, Beitr. z. path. Anat. u. z. allg. Path. **79**:700, 1928.

The work emphasizes the causation of icterus by tolylenediamine as due to capillary thrombosis of the bile-ducts rather than to damage to liver-cells. Subcutaneous injection of tolylenediamine causes a bilirubinemia with the appearance shortly of both bile pigment and bile salts in the urine. Biliary thrombi fill the biliary capillaries but the liver cells are scarcely altered.

JESSE LOUIS SERBY.

TOLUYLENDIAMINICTERUS. D. YUASA, Beitr. z. path. Anat. u. z. allg. Path. **79**:712, 1928.

Tolylenediamine gives a brownish discoloration to the blood for about twelve hours after injection, thus preventing the study of bilirubin by the van den Bergh test during that time. Dextrose administered at intervals of two hours does not delay the appearance of the icterus. The ligation of the thoracic duct in a normal animal does not give any large collection of bilirubin in the duct, whereas in an animal given tolylenediamine the ligated thoracic duct contains twice and three times the amount of bilirubin that is in the blood. The icterus caused by tolylenediamine results from a resorption of bile as well from hepatogenous and hematogenous changes.

JESSE LOUIS SERBY.

CONTRIBUTION TO THE KNOWLEDGE OF PERIARTERITIS NODOSA. S. NAUHEIM, Frankfurt. Ztschr. f. Path. **36**:32, 1928.

A case of periarteritis nodosa in which only the smallest arteries were affected and which was therefore recognized only by microscopic examination is described. Associated with the arterial lesion was malignant sclerosis of the kidney and an old pulmonary endocarditis. This association seems to support the conclusion of Fehr that a vascular poison is concerned in the production of the malignant sclerosis and to favor the idea that the periarteritis is not the result of a specific agent.

JEAN OLIVER.

ANEURYSMA DISSECANS ON A SYPHILITIC BASIS. ADALBERT LOESCHKE, Frankfurt. Ztschr. f. Path. **36**:56, 1928.

Although the etiology of dissecting aneurysms is not yet entirely clear, the author believes that in all cases a preliminary damage of the arterial wall must be assumed. The newly formed channel of the aneurysm can take on the function of the original vessel and can even undergo the same pathologic process that are observed in arteries. Ordinarily a syphilitic aortitis does not favor the development of dissecting aneurysms, but a case is described in which they occurred due to a nodular gumma in the aortic wall. The author believes that the origin of the other cases of syphilitic dissecting aneurysm reported in the literature are to be explained in a similar way.

JEAN OLIVER.

TWO RARE OBSERVATIONS IN OXYURIS INFESTATION OF MAN. HELMUTH NATHAN, Frankfurt. Ztschr. f. Path. **36**:82, 1928.

In a case of perirectal abscess oxyuris were found surrounded by a granulation tissue in which there were many foreign body giant cells. In another case of cirrhosis, ova and embryos of oxyuris were found in cystlike structures in the spleen. The location of these was explained by a retrograde passage from the portal blood stream, this being favored by the portal stasis which the cirrhosis had caused.

JEAN OLIVER.

THE HISTOLOGIC CHANGES OF THE THYMUS GLAND IN CHILDREN WITH SCARLET FEVER. P. W. SSIPOWSKY, Frankfurt. Ztschr. f. Path. **36**:123, 1928.

The weight of the thymus gland was found to be less than normal in a series of twenty-nine children who had had scarlet fever. This loss of weight was due

to a disappearance of the lymphocytes, an effect of the toxin. The lobules of the organ thus lose their typical differentiation. The medullar and cortical portion of the thymus gland both show a predominance of the reticulo-epithelial structure. There is even a proliferation of the latter formations, so that macrophage-like cells are found which are filled with fat. The picture of these changes is therefore similar to those described for other acute infectious diseases such as dysentery or diphtheria.

JEAN OLIVER.

COMPARATIVE INVESTIGATIONS OF THYROID GLANDS IN PERSONS BETWEEN THE AGES OF 25 AND 50. HANS SCHAEER, Frankfurt. *Ztschr. f. Path.* **36**:249, 1928.

For the accumulation of the normal data concerning the thyroid gland in middle Europe, only the north German coast (Kiel and Königsberg) can be considered. In all other regions endemic goiter is more or less prevalent. The weight of the organ is of little significance. Variations in the size of follicles are more important as indication of abnormality. The condition of thyroid glands in Kiel is contrasted with that of thyroid glands in Bern. Curves constructed on the age and average dimensions of the follicles in the two regions showed marked difference; nuclear changes, proliferation and desquamation of the epithelium, and other changes in the two regions are noted.

JEAN OLIVER.

### Pathologic Chemistry and Physics

STUDIES ON PERMEABILITY OF MEMBRANES. A. A. WEECH and L. J. MICHAELIS, *Gen. Physiol.* **12**:55 and 221, 1928.

In a study of the relative rates of passage through dried collodion membranes of various nonelectrolytes, it was found that acetone and urea pass through the membrane much more rapidly than glycerin, and glycerin in turn much faster than dextrose. The rate was found to vary directly with the difference in concentration on the two sides. The presence of glycerin on both sides of the membrane did not interfere with the passage of acetone. Experiments are described which suggest that with large molecules, as those of dextrose, there is a gradual clogging of the pores of the membrane until a stationary gradient is reached. The experimental data are explained on the conception of the membrane as a sieve with pores. The different diffusion rates are accordingly regarded as due to differences in molecular size, smaller molecules having a far greater pore area available for their passage than do the larger ones. It is estimated that 98 per cent of the pore area available for diffusion of acetone is unavailable for glycerin, and for dextrose only 0.3 per cent of this area is available.

A mensurative study was made of dried collodion membrane, including determinations of thickness and of relative proportions of collodion volume and pore volume. Evidence is produced that smaller molecules utilize a much larger percentage of total pore area for diffusion than do larger molecules.

H. E. EGGERS.

THE PROTEIN CONTENT OF THE CEREBROSPINAL FLUID IN MYXEDEMA. W. O. THOMPSON, P. K. THOMPSON, E. SILVEUS and M. E. DAILEY, *J. Clin. Investigation* **6**:251, 1928.

In seventeen cases of myxedema, the protein concentration of the spinal fluid was found to be high. It usually dropped to normal limits with the administration of thyroid extract. A differential point is thus given in the rare case in which myxedema may be confused with tumor of the brain or chronic nephritis.

H. R. FISHBACK.

THE PLASMA IN SEVERE DIABETIC ACIDOSIS. A. F. HARTMANN and D. C. DARROW, J. Clin. Investigation 6:257, 1928.

The composition of the blood plasma was studied in six cases of severe diabetic acidosis and also during the period of recovery. It was shown that marked concentration of the plasma occurred with but slight diminution of total base. The decrease of bicarbonate and chloride was relatively greater than the increase of ketone acid and protein. Treatment with water and insulin, with or without carbohydrate, restored the bicarbonate and  $p_H$  relatively slowly at first, and the addition of salt solution aided but little in bicarbonate recovery. The combination of sodium bicarbonate with water, insulin, carbohydrate and sodium chloride provided a rapid and complete relief from acidosis.

H. R. FISHBACK.

THE  $p_H$  OF THE URINE UNDER VITAL CONDITIONS. A. BECK and H. J. LAUBER, Klin. Wchnschr. 7:2241, 1928.

$p_H$  determinations of the urine with indicators is often without regard for the carbon dioxide tension. A shift in the  $p_H$  to a more alkaline (or less acid) reaction occurs promptly when carbon dioxide escapes, greater with alkaline urines than acid. Temperature variations also influence markedly the carbon dioxide tension and consequently the  $p_H$ .

EDWIN F. HIRSCH.

### Microbiology and Parasitology

CYTOLYSIS IN THE CEREBROSPINAL FLUID IN ACUTE POLIOMYELITIS. G. LYON, Am. J. Dis. Child. 36:40, 1928.

Cytolysis has been observed in the early pleocytoses of acute poliomyelitis, which is more active toward the multilobed elements than toward the mononuclear elements.

Proof is given of the advisability of making cell counts of the spinal fluid immediately after lumbar puncture in all cases in which there may be a possibility of poliomyelitis.

A pleocytosis consisting of 50 per cent or more of multilobed cells, occurring in a clear fluid, is suggestive of acute poliomyelitic infection. When in the course of from twenty-four to thirty-six hours, the lumbar puncture is repeated and there is a fall in the total cell count with a shifting of the differential count to a mononucleosis of 90 per cent or more, one may be certain that the condition is one of poliomyelitic infection. This cellular response is pathognomonic, as it has not been observed in the spinal fluid in other conditions.

AUTHOR'S SUMMARY.

INFECTION OF THE CONJUNCTIVA AND CORNEA OF GUINEA-PIGS FOLLOWING THE APPLICATION OF VIRULENT DIPHTHERIA BACILLI. MARGARET BEATTIE, Am. J. Hyg. 8:502, 1928.

The application of diphtheria bacilli to the previously irritated eyes of guinea-pigs for the purpose of detecting the immunity of animals immunized against diphtheria is not reliable, since 50 per cent of normal animals tested were not infected.

PEARL ZEEK.

INFECTION WITH STRONGYLOIDES STERCORALIS. J. H. SANDGROUND, Am. J. Hyg. 8:507, 1928.

Dogs and cats of all ages were successfully infected with *Strongyloides stercoralis* secured from a human patient. The animals showed certain decided differences in susceptibility to the disease and to its duration. The infections disappeared spontaneously and were followed by the acquired immunity which, in dogs, lasted for more than six months. The development of immunity was thought to be

intimately associated with the relationship that existed between the species of host and parasite and indicated the biologic maladjustment of the parasite to the host.

PEARL ZEEK.

THE PASSAGE OF LIVING BACTERIA THROUGH THE INTESTINAL WALL. LLOYD ARNOLD, *Am. J. Hyg.* 8:604, 1928.

The bacterial flora of the small intestine can be altered by diet and also by climatic changes. Disturbances in the heat regulatory mechanism of the animal cause a qualitative and quantitative difference in the flora of the upper half of the small intestine. These changes are intimately associated with an inhibition of the normal bactericidal power of the small intestine. This allows the cecal flora to ascend into the upper part of the alimentary tract, and interferes with the destruction of ingested bacteria.

Sudden alkalization of the upper part of the small intestine, in the presence of certain kinds of protein material or bile, allows viable bacteria to pass through the wall of the intestinal tract and appear for a short period of time in the thoracic duct. It is thought that these changes are brought about by alterations in the equilibrium of the autonomic nervous system.

PEARL ZEEK.

A CRITIQUE ON ARTIFICIAL PNEUMOTHORAX IN PULMONARY TUBERCULOSIS. HENRY SEWALL, *Am. Rev. Tuberc.* 18:117, 1928.

The observations set forth appear to offer solid ground for deductions as to the course of events within the thorax after complete artificial collapse of the extensively diseased left lung. While the pendular motions of the whole mediastinum and the arclike deviations of the flexible and free portions of the mediastinal pleurae have the same cause and are quantitatively similar when unmodified by adhesions, these motions are largely dissociated at a later stage of the clinical history. Comparatively early in the treatment with pneumothorax there was wide pendular swinging of the whole mediastinum. Later in the course of treatment, both movements become progressively restricted, the pendular movement to a greater degree. Moreover, the tendency to complete elimination of the pneumothorax cavity is shown by the increasing mean inclination of the mediastinum towards that side. The obliteration of this cavity must depend primarily on reexpansion of the collapsed lung, in default of which there is approximation and increased inclination of the ribs and ascent of the diaphragm on the affected side; added to which, and probably most important of all, is deviation of the plane of the mediastinum, which the stiffening and adhesions make progressively more difficult. Keeping pace with this displacement is compensatory hypertrophy of the contralateral lung.

An interesting outcome of these experimental observations was the demonstration that approximately isolated costal breathing had a marked influence on the pendular swing of the mediastinum as a whole, while pure diaphragmatic breathing had comparatively little effect. The reverse was true in the case of bulging of the flexible mediastinal pleurae, dependent on the relaxation or tautness, respectively, of the membranes with the ascent and descent of the diaphragm. With the lapse of time and progressive diminution of the pneumothorax cavity, the pendular motions of the mediastinum became relatively more restricted than the vertical motions of the lung which are activated by the diaphragm.

H. J. CORPER.

FACTORS IN THE PATHOGENESIS OF TUBERCULOSIS. ALLEN K. KRAUSE, *Am. Rev. Tuberc.* 18:208, 1928.

In following the many varied threads of this complicated and tangled skein that leads to the pathogenesis of tuberculosis, one should ever keep in mind that between the time the offending bacilli are received and that of pathogenesis, the natural history of tuberculous infection rarely discloses the disease as pursuing an uninterrupted course. Even infected infants who fall ill (and only the lesser



number do) will be found to go weeks and months with an inactive infection before a breakdown; the child months and years, and the adults years and decades. If there were no other guiding facts this circumstance alone should show that, in the majority of cases, neither native character of tissue nor kind of dosage of bacillus is decisive in establishing the pathogenesis of tuberculosis, contributory though each may be to the result. The net result of this inquiry is to suggest that from the first meeting of virulent germ and susceptible host in most cases there results a tissue graft which, if placed in the tissues of the animal man who was living a normal existence, would, because of a prompt acquisition of allergy and immunity, go the way of limited development and at last obsolescence. But civilized man has drifted far from the life of man the animal, and in the journey has been and is subjecting his ingrafted tubercle to varied forces that promote its growth and spread. Back of every awakening of tubercle, back of every nurturing of its evolution, is an experience or succession of experiences that have promoted its continued existence of progression. Common observation teaches us that such an experience, regarded physiologically, is characteristically of a stressful nature. Whatever may be stressful is to be viewed in its relations to the individual. The ultimate solution of the problem of pathogenesis of tuberculosis in human beings must be sought where the sick human being is—in the clinic—and the answer obtained from the story of the human being himself. So far, his imperfect accents all speak one way, to the effect that it is what he has done and what has happened to him since infection that have been most momentous. Environment or individual experience has swung toward or away from pathogenesis the balance formed by the initial meeting of germ and host, and soon affected by allergy and immunity.

H. J. CORPER.

**A STUDY OF TUBERCULOUS LESIONS IN THE LUNG OF A NEGRO CHILD NINE WEEKS OLD. WILLIAM SNOW MILLER, *Am. Rev. Tuberc.* 18:373, 1928.**

The lung on which this study was made was that of a negro girl, aged 9 weeks, who had been ill for six weeks. Careful reconstructions were made. The article has profuse illustration, including stereoscopic pictures. With the exception of one small area of tuberculous bronchopneumonia, miliary tubercles formed the only lesions in the region studied. The infection was conveyed from some source, as yet undetermined, through the arterial blood stream. The tubercles had developed in the capillary bed between the pulmonary artery and the pulmonary vein. The primary infection seemed to be in the lymphoid tissue associated with the pulmonary vein; this receives its blood supply from the pulmonary artery. The lymphatics were not involved in the tuberculous lesion. All the valves found in the lymphatics were situated less than 2 mm. below the surface of the pleura and opened towards the pleura. This means that from a narrow peripheral zone of the lung, the lymph must drain toward the pleura, but leaves unsettled the direction of flow from deeper portions, although it must be assumed that from the central portion the flow is toward the hilum.

H. J. CORPER.

**THE DURATION OF LIFE IN PULMONARY TUBERCULOSIS WITH CAVITY. HARRY L. BARNES and LENA R. P. BARNES, *Am. Rev. Tuberc.* 18:412, 1928.**

Of 1,454 patients with cavity which were reviewed, 80 per cent died within one year, 82 per cent within two years, 85 per cent within three years, 90 per cent within five years and 95 per cent within fifteen years. The average duration of life of 270 patients with cavities, from the appearance of the signs of cavities until death, was 15.8 months. Had the remaining survivors died on the day the statistics were compiled, it would have raised the average duration to twenty-four months. In 99 per cent of 616 cases of cavity diagnosed by roentgenogram, tubercle bacilli were found in the sputum. A family history of tuberculosis, a history of hemoptysis, or the age of the patient did not materially affect the prognosis. Only one of fifty-seven colored patients survived for three years. The average duration of life was sixteen months in males and fourteen months in females. The percentage of survivors after periods of three and five years, among patients with a pulse

rate of less than 90 was five times as great as among patients with a pulse rate of more than 100. The percentage of patients who survived for one year was more than three times as great, and of those who survived for five years was eight times as great, among patients with temperature of less than 99 F. as among patients with temperatures of more than 100 F. The survivors among patients with cavity of the right lung were slightly more numerous and lived slightly longer than those among patients with cavity of the left lung. The percentage of survivors for one and three years, respectively, was in direct relation to the amount of pulmonary disease. The duration of life bore a direct relation to the number of cavities. Of 17 patients with more than three cavities, none survived a year. Eighty-eight per cent of patients with cavities larger than 7 cm. died within a year. Among cases of small cavities (from 1 to 2 cm.) there were about 50 per cent more survivors at the end of the first year than there were in cases of large cavities (2 to 15 cm.), but 82 per cent of the patients with small cavities died within three years. Cases of honeycombed cavity were about as serious in outlook as cases of cavities of average size. Patients with well formed cavity walls had a slightly longer duration of life. Patients with well marked roentgen evidence of calcification had a greater percentage of survivors. Among patients with roentgen evidence of pleural thickening over the greater part of one lung there was a higher percentage of survivors. Of the 1,454 cases with cavities reviewed, the patients in 1,244, or 85 per cent, are dead; the average duration of life was more than twelve months.

H. J. CORPER.

TUBERCULOUS GRANULOMA OF A BRONCHUS. PHILIPP SCHONWALD, *Am. Rev. Tuberc.* **18**:425, 1928.

A case of tuberculosis is presented, in which a tuberculous laryngitis and a granuloma in the mucosa of the right bronchus, at the bifurcation, developed after a spontaneous cure of tuberculous peritonitis. The laryngitis improved greatly, but the narrowing of the right bronchus caused stagnation of purulent material in the right lung, followed by atelectasis of the right lower lobe, the spread of the infection throughout the entire right lung and, finally, spontaneous pneumothorax of the right upper lobe. The mucus, presenting almost a pure culture of tubercle bacilli, was of extreme viscosity. Its stagnation, after the pneumothorax had prevented cough, brought about asphyxiation.

H. J. CORPER.

THE REACTIONS OF THE WHITE BLOOD CELLS OF THE GUINEA-PIG FOLLOWING INOCULATION WITH HUMAN TUBERCLE BACILLI. WILL CAMP, F. H. LUTON, EDNA H. TOMPKINS and R. S. CUNNINGHAM, *Am. Rev. Tuberc.* **18**:462, 1928.

Intraperitoneal inoculations of the guinea-pig with tubercle bacilli from human beings invariably resulted in fatal infection. After inoculations of 50,000,000 or more bacilli, the tenure of life averaged three weeks; after inoculations of smaller numbers, life was irregularly prolonged. The pathologic changes in all the animals were characteristic of a generalized tuberculosis and showed three outstanding features: 1. The tissues in the early infections showed the characteristic picture of tubercle, that is, collections of monocytes and epithelioid cells which contained bacilli and were more or less intermingled with lymphocytes. 2. The tissues in the older infections presented much fibrosis, and often necrosis superimposed on the earlier single tubercles. 3. The liver invariably presented massive infection. It was consistently far more involved than is usual in tuberculous infection of the human being or the rabbit. In the older infections, the parenchymatous cells were tremendously vacuolated and filled with droplets of fat.

The blood showed definite changes following inoculation: 1. The lymphocytes decreased in number. The diminution was most marked toward exitus. 2. The monocytes increased in number and developed many of the characteristics of epithelioid cells. The increase was most marked toward exitus. 3. The magnitude of these reactions was independent of the number of bacilli with which the animals

were inoculated. 4. These reactions began earlier after inoculation when large numbers of bacilli were inoculated than when smaller numbers were inoculated. 5. These reactions were found to be an index of infection and to parallel the progress of the disease. 6. The changes in the total white cell counts and in the polymorphonuclear neutrophils bore no constant relationship to the date of inoculation, or to the reactions in the monocytes and lymphocytes.

H. J. CORPER.

THE SIGNIFICANCE OF POSITIVE AND NEGATIVE SPUTUM FINDINGS IN PULMONARY TUBERCULOSIS. MAX PINNER and WALTER I. WERNER, *Am. Rev. Tuberc.* **18**:490, 1928.

In a study of more than 500 adult patients with active pulmonary tuberculosis tubercle bacilli were found in the sputum in over 99 per cent. The absence of tubercle bacilli in the sputum of patients with pulmonary tuberculosis almost always indicates healing. Sputum free from tubercle bacilli has a much greater diagnostic and prognostic significance than is represented in the usual textbook. Every sanatorium could well invest in facilities for the complete examination of sputums from all patients.

H. J. CORPER.

CARBOHYDRATE CONTENT OF THE ALCOHOL-SOLUBLE ANTIGEN OF TUBERCLE BACILLI. KATHRYN KNOWLTON and MAX PINNER, *Am. Rev. Tuberc.* **18**:502, 1928.

The antigenic strength of the alcohol-soluble antigen of tubercle bacilli is apparently independent of both proteins and the specific carbohydrate. This fact leaves but little doubt that the antigen is of lipoid nature.

H. J. CORPER.

WATER-SOLUBLE PROTEIN AND CARBOHYDRATE IN TUBERCLE BACILLI FROM VARIOUS SOURCES. TREAT B. JOHNSON and ALICE G. RENFREW, *Am. Rev. Tuberc.* **18**:505, 1928.

Four specimens of tubercle bacilli from different sources have been examined for their content of active protein no. 304 and carbohydrate. While the yield of the protein is very low when autoclaved cells are used, the carbohydrate is still obtainable, but in reduced amounts. Both combinations apparently undergo change when the cells are heated at 100 C. or more. A technic is described for separating both fractions from a single unit of cells, and a modified technic is given for extracting the sugar fraction alone.

H. J. CORPER.

A DEATH IN CHICAGO IN SEPTEMBER, 1928, FROM INFLUENZA. EDWIN F. HIRSCH and E. R. LE COUNT, *J. A. M. A.* **91**:1186 (Oct. 20) 1928.

A case is described in which the changes in the lungs appeared to be characteristic of those observed in epidemic influenza. "The distribution of the disseminated pneumonia, the great increase in the weight of the lungs, the characteristic purple, sharply limited 'buttons' of subpleural hemorrhage, the even, thin deposit of hyaline on the lining of the smaller air passages and death on the second day all conform to the characteristic manifestations of the disease with which we became so familiar in 1918."

THE RELATION OF VIRULENCE IN PNEUMOCOCCI TO DISEASE, WITH A COMPARISON OF VIRULENCE OF THE DIFFERENT TYPES OF PNEUMOCOCCI IN VARIOUS PATHOLOGICAL CONDITIONS. C. H. WHITTLE, *J. Hyg.* **27**:412, 1928.

Lobar pneumonia, bronchopneumonia and empyema arising in previously healthy subjects are caused by strains of high virulence. Lobar pneumonia is caused by strains of the highest virulence, bronchopneumonia by strains of a rather low

virulence. Empyema is caused by strains the virulence of which is characteristic of either lobar pneumonia or bronchopneumonia. The virulence requisite for the development of lobar pneumonia in man is the same as for the development of lobar pneumonia in rabbits.

IRVING H. SCHROTH.

PROTEUS AMMONIAE. THOMAS B. MAGATH, J. Infect. Dis. **43**:181, 1928.

Detailed description is given of eighteen cultures of *Proteus ammoniae* from urine. Since the organism does not ferment dextrose, it is proposed to modify the generic characterization of the genus *Proteus*.

AUTHOR'S SUMMARY.

THE TREATMENT OF TYPHOID FEVER WITH DETOXICATED VACCINE. W. B. WHERRY, T. J. LE BLANC, L. FOSHAY and R. THOMAS, J. Infect. Dis. **43**:189, 1928.

*Bacillus typhosus* antigen can be detoxicated to a considerable degree by treating it with formaldehyde, according to Ramon's method. From about 82 to 164 millions of treated bacilli may be injected subcutaneously and daily into a patient with typhoid fever, irrespective of the apparent severity of the disease, without any harm. Twenty-eight patients with typhoid fever (bacteriologic diagnosis) were treated in this manner in Cincinnati and in Mexico City by daily subcutaneous inoculations with from 82 to 164 millions of bacilli treated with formaldehyde. The results of this treatment, along with data collected from 68 control cases, seem to show that the course of the disease is shortened, the temperature uniformly showing a tendency to drop to normal after the seventh or eighth dose and then coming to normal by irregular lysis. The average duration of the fever in the treated patients was 27.5 days, while that in the controls was 39 days. The incidence of complications seems decreased: 7 per cent in the treated, and 36 per cent in the untreated patients. Convalescence is shortened for those patients treated early in the course of the disease. The death rate is decreased from 10 per cent for the untreated to zero for the treated patients. It is to be hoped that others will help to collect enough data to make a rigid statistical analysis possible.

AUTHORS' SUMMARY.

REPLACEMENT OF POTASSIUM BY OTHER ELEMENTS IN CULTURE MEDIUMS. C. H. BOISSEVAIN, J. Infect. Dis. **43**:194, 1928.

The acidfast bacteria that were tested grew well on a simple synthetic medium. All needed potassium or rubidium for their growth; the minimum concentrations were 0.001 per cent potassium chloride and 0.002 per cent rubidium chloride.

Cesium, sodium, lithium or the radioactive elements or combinations of the two cannot replace potassium in synthetic culture mediums.

Continuous exposure to the roentgen rays for 168 hours does not kill smegma bacilli and does not favor their growth.

Among the gram-positive organisms, only a soil bacillus not previously described grew freely on the synthetic medium; it needed the same amount of potassium as the acidfast bacteria.

Among the gram-negative organisms examined, *Bacterium coli* and *Bacterium paratyphosus* B grew freely on the synthetic medium; they did not need potassium.

AUTHOR'S SUMMARY.

FILTRABLE FORMS OF THE TUBERCLE BACILLUS. FRANK B. COOPER and S. A. PETROFF, J. Infect. Dis. **43**:200, 1928.

We have failed to obtain growth from Berkefeld filtrates prepared from pure cultures of tubercle bacilli or from sputums which contain large numbers of this organism, and we have failed to observe any demonstrable tuberculosis leading to a progressive disease, either in the mothers inoculated with such filtrates or



in the offspring. We have been able, however, to demonstrate acidfast granules in such offspring, and typical acidfast organisms were found in about 36 per cent of the full grown guinea-pigs which had received filtrates. However, we have also found these acidfast organisms in the lymph nodes of 33 per cent of apparently normal animals which have never been inoculated with this material. The positive results reported by others in all probability may be due to organisms which occasionally can pass through the Berkefeld filter. Several factors may play a part in such passage, as follows: imperfect filters; the pressure used for such filtration; the medium employed, and the electro-charge of the candle.

## AUTHORS' SUMMARY.

CHRONIC LOCALIZED STREPTOCOCCUS INFECTIONS IN DOGS. G. BERNICE RHODES and CARL W. APFELBACH, J. Infect. Dis. 43:215, 1928.

Chronic abscesses were produced in the spleen and the sacrospinalis muscles of dogs by imbedding pieces of dead bone infected with *Streptococcus scarlatinae*; and in one instance with *Staphylococcus aureus*.

These focal infections resemble those occurring in human beings so far as chronicity and alternating active and quiescent periods of infection are concerned. Few complications like those occurring in human beings have so far been observed, although one dog had acute interstitial nephritis and two had iridocyclitis. We believe that this method is adaptable in many instances in which attempts are made to reproduce infectious diseases experimentally in animals.

## AUTHORS' SUMMARY.

DÖDERLEIN'S BACILLUS: LACTOBACILLUS ACIDOPHILUS. STANLEY THOMAS, J. Infect. Dis. 43:218, 1928.

Döderlein's vaginal bacillus is *Lactobacillus acidophilus*. This organism is present in less than 10 per cent of the normal vaginas of children. It gets into the vagina by exterior passage from the intestinal tract, and can be introduced into the vagina by feeding a culture by mouth. It lives and develops acid either from a secretion of the vagina, from conveyed fermentable intestinal material or from both. The organism is not present in the vagina in cases of gonococcal vaginitis. The organism has an inhibiting effect on the growth of the gonococcus in vitro; vaginal implantation of *Lactobacillus acidophilus* may present a rational cure for gonococcal vulvovaginitis and other gonococcal infections.

## AUTHOR'S SUMMARY.

STUDIES ON THE METABOLISM OF THE ABORTUM-MELITENSIS GROUP. JAMES G. McALPINE and CHARLES A. SLANETZ, J. Infect. Dis. 43:232, 1928.

By the addition of from 5 to 10 per cent of carbon dioxide to bell jars containing inoculated plates, the growth of the bovine strains of *Bacterium abortum* which had been acclimated to aerobic conditions was markedly accelerated. On the other hand, this amount of the gas had a more or less inhibitory action on *B. abortum* strains of porcine and human origin, and on *Bacterium melitensis*. This acceleration of growth for the bovine strains and inhibition for the porcine and human strains of *B. abortum* and of *B. melitensis* was apparently not due to change in the hydrogen ion concentration of the mediums. Total exclusion of carbon dioxide rendered the members of the abortum-melitensis group inert and unable to proliferate.

## AUTHORS' SUMMARY.

EXPERIMENTS RELATING TO THE PATHOLOGY AND ETIOLOGY OF MEXICAN TYPHUS (TABARDILLO). H. MOOSER, J. Infect. Dis. 43:241 and 261, 1928.

Over 90 per cent of the male guinea-pigs inoculated with the virus of Mexican typhus (tabardillo) presented more or less pronounced swelling and reddening of the scrotum, which was due to extensive specific lesions in the tunica cremasterica,

tunica vaginalis and testicles. The endothelial lining of the tunica vaginalis reacts exactly in the same manner to the presence of the virus of typhus as does the vascular endothelium. There was evidence that a considerable amount of virus was present in the swollen tunica and that it had accumulated there within the endothelial cells during the period of incubation.

A minute intracellular diplobacillus has been demonstrated in sections and smears of the proliferated tunica vaginalis of guinea-pigs reacting to the virus of Mexican typhus (tabardillo). Considerable evidence is given that this diplobacillus is the causative agent of typhus.

## AUTHOR'S SUMMARY.

RECENT CASES OF UNDULANT FEVER IN NEW YORK STATE. RUTH GILBERT and MARION B. COLEMAN, J. Infect. Dis. **43**:273, 1928.

This investigation demonstrates that cases of undulant fever are not uncommon and that they are distributed rather generally throughout New York State. In none of the cases studied was there a history of contact of patient with goats or hogs, but 14 patients were known to have used raw cow's milk. In nine instances abortions were found to have occurred in the herds from which the milk was obtained. A consideration of the data available indicates three possible reasons why cases of undulant fever are not reported more frequently in districts where unpasteurized milk is obtained from herds in which contagious abortion is prevalent. Many of the severe infections have probably been diagnosed as atypical cases of typhoid fever, influenza, or even as tuberculosis or malaria; mild forms may have presented so few symptoms that physicians have not been consulted; and the blood from some cases of undulant fever may not have agglutinated cultures of *Bacterium melitensis* or *Bacterium abortum*.

## AUTHORS' SUMMARY.

DETOXIFYING, DIFFUSING, GERMICIDAL, AND SURFACE TENSION DEPRESSING PROPERTIES OF SOAPS. FORREST R. DAVISON, J. Infect. Dis. **43**:292, 1928.

Twelve common soaps were prepared and their detoxifying, diffusing, germicidal and surface tension depressing properties were studied. Soaps possessing high detoxifying ability diffuse readily, are highly germicidal, but are correspondingly low depressants of surface tension.

## AUTHOR'S SUMMARY.

OBSERVATIONS ON THE MORPHOLOGY AND MOTILITY OF FUSIFORM BACILLI. C. C. KAST, J. Lab. & Clin. Med. **13**:112, 1928.

No evidence of spirochetal forms was seen by Kast in a pure culture of fusiform bacilli grown anaerobically in medium of varying hydrogen ion concentration containing fresh tissue. The formation of colonies and the division of fusiform bacilli were observed in a micro slide preparation. Motile fusiform bacilli, together with nonmotile forms were found in material taken directly from pathologic conditions and in mixed cultures in Schereschewsky's coagulated horse serum medium.

## S. A. LEVINSON.

THE ACTION OF VIBRION SEPTIQUE AND B. WELCHII TOXIN ON ISOLATED ORGANS. G. A. H. BUTTLE and J. W. TREVAN, Brit. J. Exper. Path. **9**:182, 1928.

Experiments dealing with the actions of *Vibrio septique* and *Bacillus welchii* toxins on involuntary muscle in vitro reveal the following facts: 1. The toxin of *V. septique* is destroyed by bubbling air, oxygen or hydrogen through its solution and its action is reversible by washing with Ringer's solution and adding a large amount of serum. 2. The concentration of toxin producing effects on smooth muscle in aerated Ringer's solution is shown to be of the same order as that in the blood of a rabbit receiving an average lethal dose. 3. A small dose of *V. septique* toxin added to a bath of oxygenated Ringer's solution containing a piece of uterus renders the tissue insensitive to the action of larger doses of either

*V. septicæ* or *B. welchii* toxin. 4. The important part of the action of the two toxins is specific in that they are neutralized only by the appropriate antisera. Titrations of the antitoxin potency of sera are described.

PEARL ZEEK.

THE PROPAGATION OF VACCINE VIRUS IN THE RABBIT DERMIS. J. C. G. LEDINGHAM and D. McLEAN, Brit. J. Exper. Path. 9:216, 1928.

A technic is described by which the vaccine virus is adapted to growth in the dermis of the rabbit and subsequently is passed successively from dermis to dermis. The growth has been measured quantitatively by titration of successive dilutions of pulp prepared from excised dermal lesions and it is shown that an inoculum by proliferation in the dermis may develop at least 100,000 times its original content of minimal infecting doses. Dermal virus, by virtue of its intrinsic freedom from bacteria, is eminently suitable for use in many spheres of the study of virus.

PEARL ZEEK.

IS *TREPONEMA PALLIDUM* A STAGE IN THE LIFE CYCLE OF THE VIRUS OF SYPHILIS? C. LEVADITI, R. SCOEHN and M. V. SANCHIS-BAYARRI, Ann. de l'Inst. Pasteur 42:475, 1928.

Histologic studies with rabbit syphilis indicate the presence of cellular inclusions with affinity for silver stain and without any morphologic resemblance to the *Treponema pallidum* during latent stages when lymphatic ganglions are demonstrably ineffective. The existence of a resistant and inapparent stage in a postulated life cycle of the *Treponema* seems to the authors highly probable.

M. S. MARSHALL.

THE BACTERIAL FLORA OF THE SPUTUM IN ASPIRATION PNEUMONIA FOLLOWING HEMOPTYSIS. A. FINKEL-KARPOVSKY, Beitr. z. klin. d. Tuberk. 69:594, 1928.

Hemoptysic aspiration pneumonia usually shows large numbers of gram-positive and encapsulated diplococci in the sputum. They are most numerous at the end of the first week and usually disappear in the fifth or sixth week. While the diplococci are present, tubercle bacilli usually disappear. The reappearance of tubercle bacilli in the sputum, while the clinical signs of pneumonia still persist, indicates the tuberculous character of the pneumonia.

MAX PINNER.

THE INFLUENCE OF RAREFIED AIR ON THE DEVELOPMENT OF EXPERIMENTAL TUBERCULOSIS IN GUINEA-PIGS. S. DEL RIO, Beitr. z. klin. d. Tuberk. 69:636, 1928.

Ten guinea-pigs were infected subcutaneously with tubercle bacilli and five of them were kept at a barometric pressure of 200 mm. below the normal; the other five were kept at normal barometric pressure. The animals which lived under normal pressure gained in weight, and showed a more extensive tuberculosis of the spleen. Otherwise there was no noticeable difference between the two groups of animals.

MAX PINNER.

MIXED INFECTION IN PULMONARY TUBERCULOSIS. G. PLATONOF and E. MOROSOWA, Beitr. z. klin. d. Tuberk. 69:656, 1928.

Secondary infection in pulmonary tuberculosis is rare and diagnosis should be made by blood culture. Even in the preagonal phase, mixed infections do not occur frequently. The temperature does not permit one to make a diagnosis of mixed infection. In order to obtain a culture of a secondary organism, the sputum must be thoroughly washed.

MAX PINNER.

TUBERCULOSIS OF THE SPLEEN AND POLYCYTHAEMIA VERA. E. SACHS, Beitr. z. klin. d. Tuberk. **69**:699, 1928.

The clinical history and necropsy observations on a patient, aged 58, are reported. The clinical diagnosis was polycythemia vera with a blood count as high as 11,000,000. The necropsy revealed a rather recent hematogenous tuberculosis of the spleen and the liver. This case leaves no doubt that the tuberculosis developed years after the polycythemia and that it did not play any causative rôle in the development of the former.

MAX PINNER.

RATIN INFECTION IN MICE AND TREATMENT WITH METALS. J. CRSKOV and ADAM SCHMIDT, Ztschr. Immunitätsforsch. u. exper. Therap. **55**:69, 1928.

The injection of salts of cesium and manganese into mice infected with ratin did not prevent the development of bacteremia. In the animals so treated improvement set in about the third day while in the untreated control animals death occurred after four or five days. The results appear to indicate a curative action by the salts.

JOHN HAYS BAILEY.

THE INFLUENCE OF THE RETICULO-ENDOTHELIAL SYSTEM ON THE PROPHYLACTIC EFFECT OF ACETARSONE (STOVAR SOL) AGAINST SPIROCHETES. P. L. RUBENSTEIN, Ztschr. f. Immunitätsforsch. u. exper. Therap. **55**:107, 1928.

In normal mice infected with *Spironema obermeieri* 92 per cent were sterilized by acetarsone after blocking of the reticulo-endothelial system with ferric saccharate; 57.5 per cent of the mice were apparently sterilized by acetarsone stovarsol but 12.7 per cent died later from relapsing fever. After splenectomy, with or without blockage of the reticulo-endothelial system, acetarsone had no therapeutic action.

JOHN HAYS BAILEY.

THE ACTION OF FILTRATES OF STREPTOCOCCI ON THE CORNEA OF THE RABBIT. O. KIRCHMER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **55**:157, 1928.

On injecting small doses of filtrates of cultures of various strains of streptococci into the cornea of rabbits, a reaction developed in the majority of instances; this consisted of clouding of the cornea, conjunctivitis and the formation of pannus. This reaction, which followed multiple injections of from 0.1 to 0.2 cc. of filtrate, diluted 1:20 (about fifty skin test doses), spaced from six to seven days apart, did not appear until after the second or third injection had been given. The conjunctivitis was usually marked, reaching its height in from two to three days. The pannus reached a climax after four or five days and slowly receded until after two to three weeks only a slight turbidity and some pannus was present.

The reaction was obtained with a commercial scarlet fever toxin, and filtrates of broth cultures of the Dochez and Riess strains of hemolytic streptococci, but not with filtrates of a broth culture of a nonhemolytic streptococcus isolated from mastitis. As control tests, the same amount of filtrate, heated at 100 C. for one hour, was injected into the cornea of the other eye. No reaction except a transient conjunctivitis resulted from these injections. The author believes that the reaction obtained was an anaphylactic response, and not due to a particular substance primarily toxic for the cornea of rabbits.

JOHN HAYS BAILEY.

### Immunology

IMMUNOLOGIC STUDIES ON VARIOUS FRACTIONS OF TUBERCLE BACILLI. MAX PINNER, Am. Rev. Tuberc. **18**:497, 1928.

Various protein, phosphatid and fat fractions have been investigated as to their immunologic behavior. The results with these chemically well defined fractions confirm essentially previous similar work done with less pure materials. Probably the most important result is the fact that a phosphatid fraction was found to be a true antigen.

H. J. CORPER.



THE VERNES FLOCCULATION TEST FOR TUBERCULOSIS: RESULTS OF 250 CASES.  
ADELAIDE B. BAYTIS, *Am. Rev. Tuberc.* **18**:513, 1928.

The Vernes flocculation test is of value in the detection of active tuberculosis. The test is of even greater value as a guide in treatment, especially in regulating the mode of life in relatively quiescent cases. When high readings are obtained in patients with doubtful diagnosis, a thorough reexamination of all the evidence is demanded. In patients who present evidence of other disease and in whom tuberculosis has not been suspected, a high reading will direct attention to the possibility of this disease, and a low reading would tend to eliminate tuberculosis from consideration. The observations on asthmatic patients under tuberculin treatment suggest a behavior which parallels that of a tuberculous patient to some extent. The Vernes flocculation test is not specific for tuberculosis in a bacteriologic sense, but it is an extremely precise and delicate test, superior to other serologic tests which have been employed in tuberculosis. It is a valuable aid in diagnosis and as a guide in the treatment of the tuberculous patient.

H. J. CORPER.<sup>6</sup>

SURFACE TENSION OF SERUM AS AFFECTED BY THE PRECIPITIN REACTION.  
SUSAN GRIFFITH RAMSDELL, *J. Exper. Med.* **48**:615, 1928.

An attempt to find evidence of a denaturing effect of the precipitin reaction on either the antigen or the immune serum, through the study of surface tension by use of the du Noüy tensiometer, yielded entirely negative results.

AUTHOR'S SUMMARY.

BACTERIOPHAGE STUDIES. RALPH S. MUCKENFUSS, *J. Exper. Med.* **48**:709 and 723, 1928.

*Mode of Action of Antibacteriophage Serum.*—Each bacteriophage is a specific antigen. The antibodies against the bacteriophage are independent of those against the bacterial substrate used in preparing the phage. The reaction of neutralization is closely analogous to that of the neutralization of toxin by antitoxin. The serum of mice experimentally infected with mouse typhoid (M.T.<sup>2</sup>) did not become capable of neutralizing phages acting on the infecting organism. The use of the reaction of neutralization of bacteriophage in the diagnosis of disease as proposed by Sonnenschein seems impractical.

*The Production of Phage from Bacterial Cultures.*—The phenomenon of phage production by one bacterial culture for another of different sort has been reproduced experimentally. This phenomenon results from phage carried with the culture, and not from the spontaneous appearance of phage in a culture previously free from it. Animals immunized against the lysogenic bacteria may develop antibodies that neutralize the phage carried. The development of neutralizing antibodies on immunization with a bacterial culture is evidence of the presence of bacteriophage in the culture. The failure of such antibodies to appear on immunization with bacteria does not necessarily indicate that bacteriophage is not present.

AUTHOR'S SUMMARIES.

ON THE INHERITANCE OF AGGLUTINOGENS OF HUMAN BLOOD DEMONSTRABLE BY IMMUNE AGGLUTININS. K. LANDSTEINER and PHILIP LEVINE, *J. Exper. Med.* **48**:731, 1928.

The heredity of two agglutinable structures demonstrable by immune agglutinins was studied in 166 families. From the data collected it is evident that one deals with a case of mendelian inheritance. The main result of the studies is the demonstration that it is feasible to investigate the heredity of serologic structures of human blood other than the group agglutinogens. Irrespective of the ultimate theory it seems probable that the properties M and N do not appear in the offspring when they are absent in both parents—a conclusion substantiated by the examina-

tion of ten families with forty-six children. These observations offer the prospect of forensic application to cases of disputed paternity and, in our opinion, a correct decision could already be given, at least with great probability, provided the reagents are available and the method properly applied. Of course, further work is needed before the test can be adopted as a routine procedure.

## AUTHORS' SUMMARY.

A PRECIPITIN TEST IN INTESTINAL SCHISTOSOMIASIS. W. H. TALIAFERRO, W. A. HOFFMAN and D. H. COOK, J. Prev. Med. 2:395, 1928.

A specific antigen was prepared by aqueous extraction of the dried livers of snails (*Planorbis guadeloupensis*) containing larval stages of *Schistosoma mansoni*. Precipitin tests of the serum of patients infected with *S. mansoni* or syphilis gave a larger percentage of positive reactions in the former. The active principle of the aqueous extract is precipitated with the albumin fraction by complete saturation with ammonium sulphate. Control antigens from the uninfected livers of snails gave negative reactions with serum from patients infected with *S. mansoni*.

AN INTRADERMAL REACTION IN EXPERIMENTAL TRICHINIASIS. GEORGE W. BACHMAN, J. Prev. Med. 2:513, 1928.

Thirty-three rabbits and twelve guinea-pigs infected with *Trichinella* showed a local skin reaction, specific in character, following the intracutaneous injection of *Trichinella* protein. The control tests with the diluent alone were negative with eight exceptions (eight tests on four rabbits). Twenty-five of the rabbits and all of the guinea-pigs, when tested before infection, gave uniformly negative skin reactions. Five normal rabbits and three normal guinea-pigs, after multiple skin tests, showed positive skin tests toward the end of the testing. These were generally rather weak, but in one guinea-pig a +++ reaction was obtained. As is evident from the tables, typical skin reactions appeared as early as the second day after infection; but in view of the fact that the preliminary skin test may have caused a local hypersensitivity, it is probably safer to conclude that typical skin reactions appear within the first week after infection. The reaction seems specific to *Trichinella* proteins since fairly negative results were obtained with *Ascaris* protein. Precipitin tests on twenty-two rabbits confirm a previous conclusion that specific precipitins are not demonstrable until from twenty to thirty days after infection. As a method of diagnosis, the skin reaction is easy and much more practical than the precipitin test since typical skin reactions appear from twenty to thirty days before the precipitins are demonstrable in the blood stream.

## AUTHOR'S SUMMARY.

EXPERIMENTAL SENSITIZATION PER VAGINAM WITH PROTEINS FROM MALE GONADS. DAVID I. MACHT, J. Urol. 20:733, 1928.

After a successful series of experiments on sensitization of guinea-pigs by instillation of blood serum into the vagina were performed, a series of experiments were made with instillations of fresh prostatic and testicular emulsions and positive evidence of sensitization produced in guinea-pigs in this way has been obtained.

## AUTHOR'S SUMMARY.

THE TREATMENT OF PULMONARY TUBERCULOSIS WITH A RESIDUAL ANTIGEN. C. E. JENKINS, Brit. J. Tuberc. 22:126, 1928.

The author prepares a residual antigen from cultures of human and bovine strains of tubercle bacilli by a rather elaborate method of ether extraction, sodium hydroxide digestion and treatment with pepsin and hydrogen peroxide. The antigen does not cause inoculation abscesses, and the immediate clinical results approach those obtained with the residual antigens of other organisms. In approximately two thirds of all cases of pulmonary tuberculosis, it is believed, appreciable benefit can be obtained from this antigen. The duration of improvement is at present unknown. For details, the original paper should be read.

H. J. CORPER.

THE ACTION OF ULTRA-VIOLET RAYS ON THE SKIN. ALBERT EIDINOW, Brit. J. Tuberc. **22**:136, 1928.

The present conception of the action of ultraviolet rays on the skin supports the theory of the production of (1) local photobiochemical substances which have bactericidal or vitamin properties; (2) local hyperemia of the skin; (3) stimulation of a leukocytic infiltration of the epidermal tissues.

H. J. CORPER.

IMMUNIZATION AGAINST CHICKENPOX. K. v. KÉSMÁRSZKY, Arch. f. Kinderh. **85**:1, 1928.

Immunization was effected by intracutaneous injection of 0.1 cc. of citrated blood from a patient with chickenpox within thirty-six hours of appearance of the disease. The duration of this immunity was not determined.

SERUM REACTIONS WITH MIXTURES OF ALCOHOLIC EXTRACTS OF ORGANS AND HOG SERUM. LYDIA HENNIG, Ztschr. f. Immunitätsforsch. u. exper. Therap. **55**:19, 1928.

A large number of guinea-pigs were injected with mixtures of alcoholic extracts of guinea-pig kidney and hog serum, but it was not possible to detect antilipoid immune bodies by the Wassermann, Sach's-Georgi or Menicke reactions. The animals were hypersensitive to mixtures of guinea-pig lipid and hog serum after an interval of three and one-half weeks and reacted strongly, even with lethal shock, to doses which were without effect on animals treated with extract or serum alone or on normal animals. Thus the same results were obtained by use of the native lipoids as Klopstock obtained with foreign lipid preparations and interpreted as lipid anaphylaxis.

JOHN HAYS BAILEY.

BRESLAU INFECTION IN MICE. J. ORSKOV, K. A. JENSEN and KENJI KOBAYASHI, Ztschr. f. Immunitätsforsch. u. exper. Therap. **55**:34, 1928.

Breslau bacilli administered orally or intravenously cause a bacteremia that is fatal. Vaccination with killed organisms protected the mice, although vaccinated mice may become carriers of the infection. Intracellular destruction of the organism occurs more rapidly in the vaccinated than normal mice.

JOHN HAYS BAILEY.

CONTAMINATION OF ISO-AGGLUTININATIVE SERUM BY BACILLI THAT PRODUCE AGGLUTININ. V. FRIEDENREICH, Ztschr. f. Immunitätsforsch. u. exper. Therap. **55**:84, 1928.

The bacillus found by Thomsen to cause agglutination of human corpuscles is not agglutininative by itself, but agglutinin is present in the filtrates of broth cultures of the bacillus. In contaminated serum, this agglutinin may be present side by side with alpha and beta agglutinins. In 500 samples of blood, 18 instances of contamination were observed; in 11 the bacterium was isolated (in 9 bacillus "M," in 2 bacillus "J").

JOHN HAYS BAILEY.

ON CHEMOSPECIFIC ANTIGEN. A. KLOPSTOCK and G. E. SELTER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **55**:118, 1928.

Diazotized serum was used as antigen. The corresponding antiserum reacted by fixation and precipitation with diazotized serum from various species but most strongly as a rule with the serum of the homologous species. Chemospecific antigens can be prepared in a similar way with atoxyl and serum or with atoxyl and *B. proteus* X 19.

JOHN HAYS BAILEY.

AGGLUTINATION OF PARATHYPHOSUS B AND ENTERITIDIS. BRESLAU. M. FISCHER and FRAULEIN GROSSMAN, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **55**:142, 1928.

*Bacillus paratyphosus* B Schottmüller and *B. enteritidis* Breslau may be differentiated by agglutination with their antisera in 8.77 and 17.54 per cent sodium chloride solutions. Breslau serum gives a double agglutination, while Schottmüller serum agglutinates only its antigen. If the  $p_H$  be varied, using physiologic solution of sodium chloride, a double agglutination is obtained with Breslau serum in all ranges, while an anti para B serum agglutinates the Breslau organisms only in the acid range.

JOHN HAYS BAILEY.

AGGLUTININ AND PRECIPITIN IN ANTICHOLOERA SERUM. E. HOEN, L. TSCHERTKOW, W. ZIPP, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **55**:149, 1928.

The vibrios absorb the agglutinin in anticholera serum, leaving a precipitin that reacts with filtrate of cultures of the cholera vibrio. This precipitin resists heating at 57° C. for one hour.

JOHN HAYS BAILEY.

### Tumors

ANALYSIS OF 176 CASES OF CARCINOMA OF THE STOMACH SUBMITTED TO AUTOPSY. M. WARWICK, *Ann. Surg.* **88**:216, 1928.

In 7,800 necropsies there were 570 carcinomas, of which 176 were carcinoma of the stomach. The disease is more frequent in males. Thirty-nine per cent occurred in the sixth decade and 29 per cent in the fifth decade; 42 per cent were in the pylorus, 37 per cent in the wall and 11 per cent in the cardia. Ten per cent were diffuse; 43 per cent ulcerated, and of these 51 per cent were perforated, 16 per cent closed off and 35 per cent open, causing fatal peritonitis. Obstruction was present in 34 per cent; in the great majority, at the pylorus. Metastases were found in 77 per cent—liver, lymph nodes, peritoneum, omentum, lungs, mesentery, bronchial lymph nodes. Emaciation was marked in 62 per cent and moderate in 20 per cent.

N. ENZER.

A STUDY OF EPITHELIAL NEOPLASMS OF THE URINARY BLADDER. KENNETH FRATER, *J. Urol.* **20**:371, 1928.

The so-called benign papilloma should be classified as epithelioma of low grade malignancy. With few exceptions, malignancy does not increase with recurrence. The grading of a specimen removed cystoscopically can be relied on. The specimen reported to be inflammatory tissue should be examined several times before exclusion of malignancy is justifiable. Epithelioma of the bladder does not show variation in grade of malignancy in different parts of the same tumor.

AUTHOR'S SUMMARY.

SMALL CARCINOMAS OF THE PROSTATE GLAND. EDWIN F. HIRSCH and LOUIS E. SCHMIDT, *J. Urol.* **20**:387, 1928.

The results reported here emphasize again the need of a careful microscopic examination of tissues from many places of the prostate gland removed with the clinical diagnosis of benign enlargement in order that small malignant growths do not escape notice.

AUTHORS' SUMMARY.

ROENTGEN SARCOMA. H. J. ALIUS, *Beitr. z. klin. chir.* **143**:567, 1928.

Alius relates the case of a man who submitted to roentgen treatment of a lupus vulgaris for seventeen years and then developed a sarcoma on the site exposed to the rays. The tumor grew rapidly and finally was excised surgically.



A year later, there was a recurrence. Neither the first nor the second specimen was proved to be malignant. Four months after the second excision, the growth had recurred. Microscopic examination showed it to be a spindle cell sarcoma. A fourth recurrence was excised two months later. By the end of the month the patient complained of pains in the abdomen. The previous site of the disease was the supraclavicular region. Pain, emaciation and bloody stools followed in rapid succession. The roentgen examination with barium showed an involvement of the ascending colon. Then came dyspnea, radial paralysis of one hand and mental symptoms. Inside of three months death occurred, eighteen months after the patient first noticed a tumor. The necropsy disclosed multiple metastases in the intercostal and pectoral muscles, pleura, lungs, ileocecal lymph nodes, cecum and left temporal lobe of the brain. Admitting that the lupus had some connection with the reason for the development of the sarcoma, the author is of the opinion that the main cause was the long continued roentgen irradiation. The case is particularly interesting in that it is the only one of sarcoma following roentgen irradiation in which it was possible to follow the development of the growth histologically from its inception as an ulcer to the appearance of its malignant nature.

### Medicolegal Pathology

THE ELIMINATION OF NICOTINE IN MILK. R. A. HATCHER and H. CROSBY, *J. Pharmacol. & Exper. Therap.* **33**:1, 1927.

Characteristic physiologic responses are obtained when nicotine in as small a ratio as 1:500,000 is injected into the lymph sacs of frogs. Still smaller quantities may be recognized by the odor when concentrated and pure extracts are made alkaline. It was found that lactation was markedly lessened or altogether checked in cows and cats by nicotine; although abundant, at first, in a primipara accustomed to smoking from twenty to twenty-five cigaretts a day, the flow of milk quickly diminished. The smoking of seven cigaretts in two hours caused a marked subsidence. In purified extracts of the milk, nicotine was easily demonstrated. The effect on nurslings has not been investigated.

E. R. LE COUNT.

THE LOCALIZATION OF BARBITURIC ACID COMPOUNDS IN THE BRAIN. E. KEESER and J. KEESER, *Arch. f. exper. Path. u. Pharmacol.* **125**:251, 1927.

These investigators were unable to obtain from, or demonstrate the presence of luminal, veronal and other compounds of barbituric acid in the cerebral hemispheres, mesencephalon, cerebellum, pons or medulla; but they did find them in the thalamus and corpus striatum. These parts of the brain, therefore, should always be examined for hypnotic poisons.

The investigations, however, were undertaken because of different views which are held regarding sleep and its possible regulation by particular regions of the brain. Compounds of these barbituric acid derivatives were made with both iron and silver and recovered in their original crystalline form by chemical methods from the brains of rabbits. They were also found microscopically in the aforementioned basal ganglions by appropriate histochemical methods but not elsewhere. The conclusion by these investigators about sleep and a nerve center for its control are very reserved. They do not, for example, maintain that hypnosis due to drugs and natural sleep are necessarily brought about in the same way.

E. R. LE COUNT.

CHRONIC POISONING WITH WOOD ALCOHOL. A. LEO, *Biochem. Ztschr.* **191**:423, 1927.

Experiments were made with dogs. Both synthetic methyl alcohol as well as the usual form were used; no difference was found in their action. The lethal dose for dogs is 8 cc. per kilogram. After repeated intoxications, this dose was easily borne. One dog weighing 12.5 Kg. received 1 liter of 97 per cent methyl alcohol during seven weeks. Not even a fatty liver was produced, an effect of

wood alcohol which many have regarded as quite constant. No albumin, sugar or biliary pigments appeared in the urine.

Methyl alcohol is burned to formic acid in the body, and this appears in the urine as formates. With tolerance established, the excretion of formic acid appreciably lessened. For this outcome, no entirely satisfactory explanation is given. Among those offered are the excretion of methyl alcohol unchanged, increased ability to exhale the poison or oxidize the formates, and resorption of the alcohol and its products from the urinary bladder. This lessening of the formic acid in the urine has been noted before and as a result not only of repeated poisonings with methyl alcohol, but also a consequence of poisoning with ethyl alcohol with or previous to the administration of wood alcohol.

Apparently tolerance for one confers tolerance for other alcohols. Considerable difficulty was experienced in distinguishing between the results of a true chronic poisoning and repeated acute poisonings with wood alcohol. The degree of toxicity is largely directly proportionate to the concentration. The small amount of wood alcohol in the smoke of tobacco, as tobacco is smoked in pipes, cigars, etc., is quite harmless. There is only about 42 mg. in the smoke of 70 Gm. of tobacco.

E. R. LE COUNT.

FATAL EMPHYSEMATOUS GANGRENE AFTER PROBING A GRAVID UTERUS. E. M. FUSSE, *Zentralbl. f. Gynäk.* **52**:116, 1928.

A woman, aged 39, wore a silver, cervix-occluding pessary which a physician removed for each menstruation. On one occasion, the physician being away, the husband removed it. When the uterus was found enlarged, a few days later, a tumor was suspected. A sound was introduced; eight hours later there was a severe chill; twelve hours later, death. A short, plump, gram-positive bacillus, with the characteristics of the bacillus of emphysematous gangrene, was obtained from the blood during life and from many places after death. When the pessary was removed, a little brown fluid escaped. It is suggested that the sound carried into the uterus the anerobic bacteria from a latent infection caused by wearing the pessary.

E. R. LE COUNT.

IS THE ABDERHALDEN TEST OF VALUE FOR MEDICOLEGAL PURPOSES EARLY IN PREGNANCY AND IN ABORTION? M. KERNBACH and D. BERARIU, *Ztschr. f. ges. Genschbl. Med.* **12**:487, 1928.

With the Abderhalden test, positive results may be obtained during the entire course of pregnancy, from the first weeks and for ten days after birth. The test may be positive in extra-uterine pregnancy. Positive results may be obtained after abortion, but only for about fourteen days.

### Technical

DIFFERENTIAL DIAGNOSIS OF SURGICAL FROM NONSURGICAL JAUNDICE BY LABORATORY METHODS. LUCIUS W. JOHNSON and PAUL F. DICKENS, *Am. J. M. Sc.* **176**:690, 1928.

Laboratory indications for surgical intervention are: (a) persistent and increasing jaundice, with a direct immediate van den Bergh reaction; (b) dye retention, and (c) absence of bile or dye from duodenal contents. In obstructive jaundice the delay in the elimination of bromsulphalein is definite and of great value in diagnosis when taken in conjunction with the van den Bergh test. In malignant conditions of the liver it is of value in determining the amount of damage to the liver tissue.

PEARL ZEEK.

THE RESORCINOL FLOCCULATION TEST FOR ACTIVITY IN TUBERCULOSIS. ADELAIDE B. BAYLIS and WARD J. MACNEAL, *Am. Rev. Tuberc.* **18**:843, 1928.

The resorcinol test is without any claim to specificity in a bacteriologic sense, but it offers some help in determining activity or arrest of the tuberculous process.

In the known tuberculous person it is a convenient and reasonably reliable method of measuring the state of activity of the tuberculous process, and it is in such cases that it would seem to have its greatest promise of usefulness. The simple test of Baylis is described, and results with its use are recorded. It obviates the use of the expensive photometer of the Vernes test. Five tenths cubic centimeter of the 1.25 per cent resorcinol solution is gently poured on to 0.5 cc. of the patient's serum in a small tube, the mixture is then rapidly passed from one tube to another and back again, and the container is closed with a rubber stopper and allowed to remain in the room four hours, and in the refrigerator over night. In the morning it is again placed in the room without shaking and allowed to rest until the water of condensation has disappeared from the exterior of the tube. Reading by the naked eye is recorded as —,  $\pm$  to ++++ or atypical, according to the quantity and quality of the sediment.

H. J. CORPER.

**DIFFERENTIAL MEDIUM FOR SALMONELLA PULLORUM, SALMONELLA GALLINARUM, PASTEURELLA AVICIDA AND ESCHERICHIA COLI.** W. L. MALLMANN and SNYDER, *J. Infect. Dis.* **44**:13, 1929.

A dextrin-lactose agar slant medium for the differentiation of the bacteria mentioned is described.

AUTHORS' SUMMARY.

**THE TECHNIC OF OPERATION ON MICE.** WERNER KOOSE, *Centralbl. f. Bakteriolog.* **106**:140, 1928.

This article describes and illustrates certain procedures and operative methods of value in various operations on mice, such as preliminary and postoperative care, types of narcosis, technics for castration, suprarenalectomy, decerebration, etc.

PAUL R. CANNON.

**CREATININE ESTIMATIONS OF THE BLOOD (ONE THOUSAND ANALYSES).** F. LICKINT, *Klin. Wchnschr.* **7**:2341, 1928.

Creatinine increases fairly regularly with the total nonprotein nitrogen, but unexplained individual deviations from this do not permit the substitution of the complicated nonprotein nitrogen determinations by the simpler creatinine estimations.

AUTHOR'S SUMMARY.

**SIMPLIFICATION OF THE HOHN CULTURAL DEMONSTRATION OF B. TUBERCULOSIS.** F. E. LOEWY, *München. med. Wchnschr.* **75**:2096, 1928.

Thick-walled centrifuge tubes (12 cc.) are provided with several small glass beads, stoppered with a cork and sterilized dry. About 1 to 1.5 cc. of sputum is transferred into the tube which is then filled with 10 per cent by volume of sulphuric acid, stoppered, vigorously shaken, placed horizontally for twenty minutes and centrifugated. Two tubes of egg medium are inoculated with the sediment and are examined from time to time after two weeks by stained preparations.

EDWIN F. HIRSCH.

**THE PROGNOSTIC VALUE OF INDICAN IN THE BLOOD SERUM IN NEPHRITIS.** A. KROKIEWICZ, *Virchows Arch. f. path. Anat.* **266**:239, 1927.

The author found increased indican in the serum, a more reliable diagnostic and prognostic test in nephritis than an increase in nonprotein nitrogen or in other substances. The Jolles-Haas test for indican was found to be simple and reliable, and its use is recommended in all cases of nephritis. The test was negative in fifteen patients with acute nephritis, all of whom recovered without uremia. In twenty-five cases of chronic nephritis, uremia developed in nine patients with positive indican tests but was absent in sixteen with negative tests.

B. R. LOVETT.

## Society Transactions

### PHILADELPHIA PATHOLOGICAL SOCIETY

*Regular Meeting, Nov. 8, 1928*

J. HAROLD AUSTIN, M.D., *Presiding*

#### THE RÔLE OF ALLERGY IN TUBERCULOSIS. (ABSTRACT OF ANNUAL GROSS LECTURE.) ARNOLD R. RICH.

The lecture was concerned with the precise definition of bacterial allergy, and the rôle which this phenomenon plays during the course of tuberculous infection.

In the discussion of the character of the local allergic tissue reaction, it was pointed out that accelerated tubercle formation should not be regarded as a form of the allergic reaction, and that any local fixation of bacilli which may occur in the immune body is more probably a result of specific precipitation than of the inflammation of allergy.

Tissue culture experiments demonstrating that allergy consists in a cellular change were described. It was shown that no plasma antibody is necessary for the injury and death of allergic cells exposed to tuberculoprotein.

Principles established by experiment concerning the interrelation of allergy, dosage, virulence and resistance were discussed; it was shown how the application of such principles enables one to interpret more accurately the pathogenesis of lesions observed at autopsy. The lesions characteristic of acute caseating miliary tuberculosis and of tuberculous meningitis were used as examples. In the discussion of the latter lesion it was pointed out that tuberculous meningitis cannot be produced by direct blood stream infection of the meninges, but that it depends on the establishment of local caseous foci from which bacilli may be discharged directly into the meninges or the ventricular cavities.

The relation of allergy to acquired resistance was discussed, and evidence was presented against the current view that allergy is the mechanism of acquired resistance. This evidence, while by no means conclusive, is sufficient to warrant a thorough inquiry into the question as to whether allergy is necessary for the operation of immunity in tuberculosis. Up to the present time, no one has proved that it is necessary in tuberculosis, even though it may be of service in other infections in which the blood plasma possesses demonstrable bactericidal or lytic properties, or the phagocytes marked bactericidal powers. If allergy is not necessary for immunity, procedures directed toward desensitization might be of considerable value in certain cases, for the necrotizing activity of allergy is well known to be responsible for the greater part of the tissue destruction observed in tuberculosis. Clinical evidence was cited indicating that treatment with tuberculin is effective especially in the instances in which desensitization is produced. Tuberculin therapy carried out from the standpoint that desensitization permits repair by restoring the tissues to their normal indifference to tuberculoprotein, and so preventing necrosis of encapsulating granulation tissue, is different in theory and method from that carried out from the standpoint that the production of focal inflammatory reactions about lesions promotes their healing. It is urgent to determine by experiment whether or not allergy can be abolished while resistance remains intact. There is evidence that it can be, but further work is necessary to settle the question in tuberculosis as well as in all other infections. Experiments in progress indicate that a high degree of acquired immunity can be demonstrated in the absence of allergy in certain other infections.

Acquired immunity in tuberculosis may depend on factors similar to those operating in natural immunity rather than on a specific bactericidal mechanism. Certain characteristics of natural immunity were discussed, but further work is necessary for the understanding of just what it is that inhibits free parasitism in natural immunity. The theory that natural immunity is a result of a rapid and vigorous cellular attack on the invading micro-organism is untenable.



## NEW YORK PATHOLOGICAL SOCIETY

*Regular Meeting, Dec. 13, 1928*HARRISON S. MARTLAND, *President, in the Chair*

## FATAL FAT EMBOLISM. B. M. VANCE.

Fat embolism is the name given to the condition which occurs when globules of liquid oil appear in the circulating blood and lodge in the smaller vessels and capillaries throughout the body. The effect of this process on the system depends on the number and distribution of the emboli. In most instances they are few, and little disturbance takes place. In the occasional case, however, many may be present, and serious and even fatal complications follow their appearance.

Almost all fatal cases of fat embolism are the result of injuries involving fatty tissues, such as fractures of the shafts of the long bones, severe injuries to the subcutaneous fat, or orthopedic manipulations of the lower extremities. Traumas of this sort may set free much liquid fat from the cell envelopes and rupture many small venules in the immediate vicinity, so that a large amount of oil may be aspirated into the venous circulation. Immediately after this, fat emboli appear in the pulmonary vessels.

Gröndahl (*Deutsche Ztschr. f. Chir.* **111**:56, 1911) described two clinical varieties of fat embolism.

1. The first type is known as pulmonary fat embolism and is found in persons whose cardiac musculature is weak. The emboli appear in large numbers in the pulmonary arterioles and capillaries and interfere with the passage of the blood through the lungs. The right ventricle of the heart is not strong enough to force the oily plugs onward into the systemic circulation, and the patient, after an interval of several hours during which he is free of untoward symptoms, dies of acute asphyxia and cardiac collapse.

The following case is a good example of this condition.

CASE 1.—A white man, aged 62, sustained fractures of the right femur, right tibia and right fibula in an automobile accident. He survived for thirty-six hours, dying in a severe asthmatic attack with definite signs of pulmonary edema.

The necropsy disclosed large edematous lungs which, on microscopic examination with osmic acid and sudan III, revealed numerous fat emboli in the pulmonary vessels and capillaries (fig. 1). A few others were found in the myocardium, kidneys and brain, but were of slight consequence. In addition, a moderately enlarged heart, an appreciable coronary arteriosclerosis, chronic interstitial nephritis, hydronephrosis, hypertrophy of the prostate and senile atrophy of the brain were present. It was evident from the examination that the oil globules in the blood vessels of the lungs had overtaken a heart already weakened by a chronic cardiorenal condition.

2. The second type is found usually in those persons whose right ventricles are strong enough to drive the fat from the pulmonary vessels into the general circulation. The emboli are carried to the different organs of the body in large numbers. As many of these invaders reach the brain and evoke characteristic symptoms, this variety is known as cerebral fat embolism.

Clinically, these cases show an interval of from thirty to forty-eight hours after the injury that is free from noteworthy symptoms except slight restlessness and dyspnea. The patient then lapses gradually into coma, which becomes deeper and deeper until death occurs several days later.

Cotemporary with the onset of the coma, the skin of the upper part of the chest, the shoulders and the front part of the neck shows numerous petechial hemorrhages which tend to gather into small groups of six or seven. Gröndahl declared that these lesions are the result of fat emboli lodging in the skin.

The following three cases are typical.

CASE 2.—A white man, aged 25, was injured in an automobile accident, fracturing the shaft of the right femur. Thirty hours later, he lapsed into coma in which he remained until his death five days later. Numerous petechial hemorrhages were present in the skin of the chest.

CASE 3.—A white woman, aged 45, sustained an extensive fracture of the right tibia and fibula in an automobile accident. There was a gradual lapse into coma two days later, and she remained in this state until she died four days after the injury. Petechial hemorrhages were also noted in the skin of the upper part of the chest.

CASE 4.—A white woman, aged 47, incurred fractures of both clavicles and a few ribs and, in addition, an extensive injury to the subcutaneous fat about the

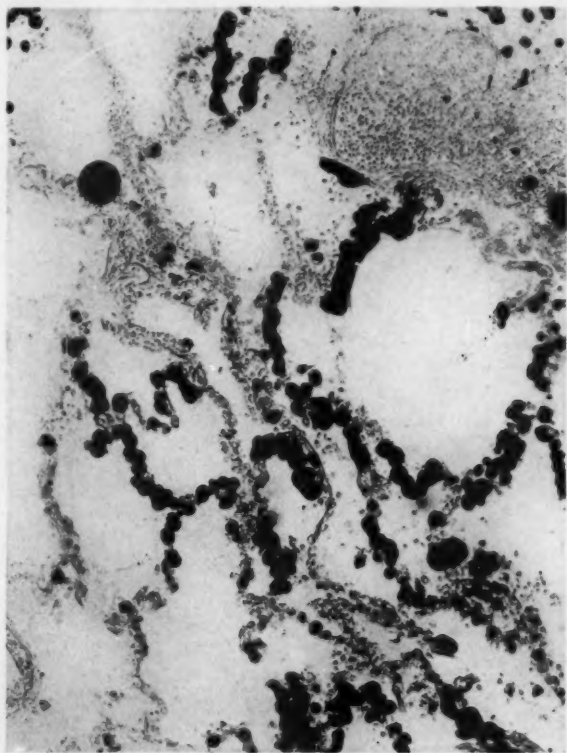


Fig. 1 (case 1).—Fat emboli in the pulmonary capillaries. Osmic acid stain.

left knee in an automobile accident. Aside from the notation that she died in coma four days after the trauma, a clinical history was not obtained.

All three cases, however, showed practically similar lesions at necropsy.

The lungs were congested and edematous. In all, a slight peribronchial pneumonia was present. Minute hemorrhagic infarcts were noted in case 3. Fat emboli were demonstrated in the smaller arterioles in large numbers, but were not as evident in the capillary network.

Parenchymatous organs like the liver and kidneys did not show definite pathologic changes, though fat emboli could be demonstrated readily enough by microscopic examination. In the kidneys they appeared as characteristic pretzel-like coils in the glomerular tufts (fig. 2).

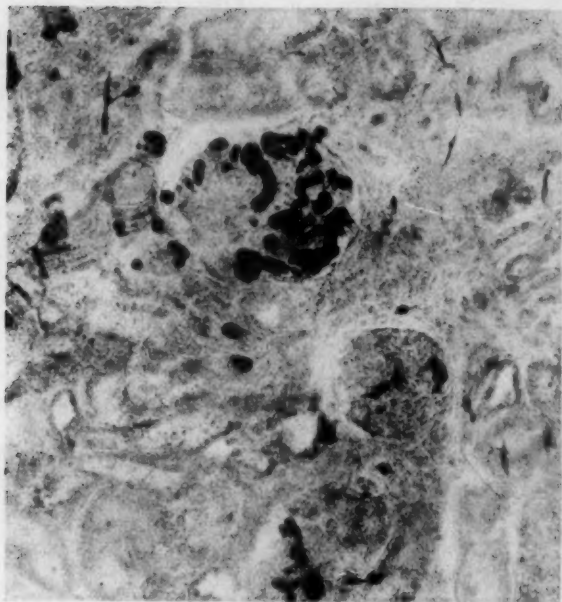


Fig. 2 (case 4).—Fat emboli in glomeruli of kidney. Sudan III stain.



Fig. 3 (case 4).—Petechial hemorrhages in brain caused by fat emboli.

On macroscopic examination, the heart muscle was permeated by small streaky hemorrhages, from 2 to 4 mm. in diameter. Microscopic examination disclosed that the small arterioles in such areas were plugged with a sausage-shaped oil globule. The muscle fibers immediately adjacent were atrophic, filled with small fatty granules and surrounded by red blood cells. The lesion caused by the embolus had all the characteristics of a minute hemorrhagic infarct.

The brain showed numerous petechial hemorrhages, quite prevalent in the white matter, but infrequently found in the gray matter (fig. 3). Fat emboli were discovered in the small arterioles in the midst of the hemorrhagic areas, while around the vessel was a zone of necrosis in which were grouped red blood cells and a few lymphocytes and leukocytes, mixed in with a collection of large ovoid cells, presumably of glial origin (fig. 4). The lesion was undoubtedly a minute infarct caused by the fat embolus.

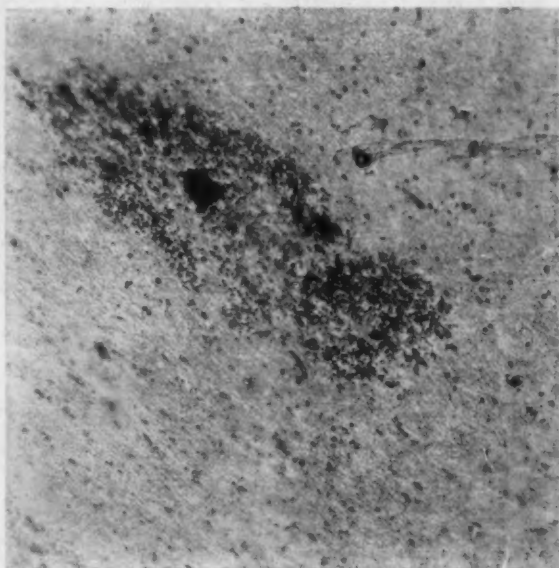


Fig. 4 (case 4).—Lesion produced by a fat embolus in an arteriole of the brain. Osmic acid stain.

Apparently the liquid fat, after passing into the systemic circulation, literally bombarded the brain in the form of thousands of minute emboli. This in itself is sufficient to explain the rather dramatic lapse into coma which later ended in death.

#### DISCUSSION

HARRISON S. MARTLAND: I have been very much interested in fat embolism for many years and did not believe until recently that it was a serious lesion. Roswell Park in 1884 was the first American surgeon to call attention to the danger of fat embolism after traumatism to the long bones. During the war, Bissell, of the Mayo Clinic, again called attention to the fatal outcome in some cases of fat embolism. He claimed that he could often suspect fat embolism by the gross appearance of the organs at autopsy. He advised a special autopsy technic for opening the right side of the heart and the lungs to avoid contamination. In a few patients with clinical pictures of so-called surgical shock dying after operative procedures on bones, amputation of the breast for cancer and the surgical cure



of umbilical hernia in the obese, he found fat globules in the blood of the right side of the heart and an extreme bloody engorgement of the lungs, which blood showed oil droplets. During the war, Dr. Robertson and myself in Paris, did not give great credence to the seriousness of fat embolism. Since this time there has been considerable discussion as to how important it is as a cause of death. In some of my recent work on traumatic cerebral hemorrhages of the multiple, punctate variety (ring hemorrhages which I have attributed to concussion), I mentioned the fact that it was almost impossible at times to know whether fat embolism did not play an important etiologic factor in these cases. In the development of the "Punch drunk" theory the same question came up, so I am greatly interested in Dr. Vance's demonstration. I would like to know how often in his medicolegal work he is able to attribute death to fat embolism; whether he recognizes it grossly, and whether in systemic fat embolism he has noted the patency of the foramen ovale.

Askanazy has reported multiple punctate hemorrhages in the white matter of the brain following a simple fracture of the femur in which he found a patent foramen ovale. He thought systemic fat embolism was much more apt to occur when the foramen was open, as otherwise the lungs filtered out most of the fat. The frequent occurrence of the lesions in the white matter and deeper portions of the brain and their absence or scarcity in the gray cortex may also be explained on mechanical grounds, as fat droplets will more readily enter the central ganglionic system of vessels than the cortical, and when they enter the cortical vessels are much more apt to lodge in the long medullary arteries of the cortical system which supply the centrum ovale. According to Bissell, fat entering the venous circulation markedly increases the viscosity of the venous blood and results in a rise in venous pressure and a fall in systolic, hence the resemblance to surgical shock.

JAMES EWING: As far as I know, it is a long time since any definite additional knowledge has been thrown on the pathology of fat embolism. Therefore, I feel one can congratulate Dr. Vance on having subdivided cases into those in which the main disturbance is in the pulmonary circulation and others in which it must be in the systemic circulation, particularly in the brain. That is, I believe, a new point of view, and a definitely new contribution. I would raise the question whether in addition to the weakness of the heart the quantity of fat concerned in the embolism might not have an important bearing on the course of the case. I have had the opportunity to examine a group of animals in which oil had been injected into the circulation; in these the main lesion was in the lungs; fat could be found in the lungs in great quantity, and death was by asphyxia. I think the cardiac power was presumed to be normal here, and I simply raise the question whether the quantity of fat may have something to do with the fate of the case, as well as the character of the circulation; yet I am quite prepared to accept Dr. Vance's explanation as to the activity of the power of the right ventricle.

B. M. VANCE: I think cases of fat embolism which have a fatal termination are rare. Less than ten have been noted among our Medical Examiners' cases of the past ten years.

In my series of cases an obviously open foramen ovale was not present but was either closed or open by such a small slit that it was improbable that much liquid fat was forced through this opening. It is my own opinion that in the cases of cerebral fat embolism most of the emboli were forced through the pulmonary capillaries into the systemic circulation.

The point raised by Dr. Ewing is interesting. The amount of liquid set free around the site of a recent fracture probably amounts to about 4 ounces of fat mixed with blood. I think in the majority of instances that the human organism is not seriously embarrassed by the fat immediately absorbed into the pulmonary circulation from the site of such an injury. The absorption is usually gradual, and if the torn venules in the injured area close rapidly, the absorption will cease. It is only rarely that an amount of liquid fat at all comparable to the amount of oil injected into the veins of experimental animals enters the pulmonary capillaries of the human patient. When this does occur, death takes place just as rapidly.

## METASTASIZING ADENOMA OF THE THYROID. FREDERICK H. MCKEE.

There is a definite group of epithelial tumors of the thyroid gland which present a benign histologic picture and run a relatively benign course. They metastasize to bone characteristically, but the route of metastasis and the duration of the secondary tumors differ from the other malignant epithelial tumors of the thyroid. Connheim, in 1876, was the first to separate this type.

Mrs. G. M., aged 45, entered St. Luke's Hospital, Nov. 23, 1922, because she suddenly vomited a pint of bright blood. She had had a goiter for many years but enjoyed good health until four years before admission, when she began to have moderate dyspnea on exertion. Physical examination revealed a large, irregular thyroid gland and dulness to percussion for 8 cm. below the manubrium sterni. Roentgen examination showed increased density in the upper mediastinum, dilatation of the entire esophagus and displacement of the trachea to the right.

Five years later the patient was readmitted to the hospital complaining of a painful lump beneath the right breast, which had been present for at least three years. At this time a growth in the rectum was found which proved to be a squamous type of epithelioma. She died six months later, emaciated, cachectic, dyspneic, and suffering constant pain because of chronic obstruction from the rectal tumor.

At autopsy the thyroid gland was irregularly enlarged and firmly adherent to the anterior and lateral aspects of the trachea, and its base was adherent to the aortic arch. A thick fibrous capsule enveloped the gland. The greater part of the cut surface was smooth, pale brown and translucent, with scattered hemorrhagic and calcified areas. A circumscribed nodule, 4.6 cm. in diameter, was situated in the upper right lobe. Its surface was tan, opaque, of velvety smoothness and separated into lobules. The fifth right rib was the site of an ovoid tumor measuring 10 by 5 by 4 cm. It was situated 7 cm. from the costochondral junction and completely replaced bony tissue. On section, the surface was tan-colored and smooth, its appearance being identical with the tumor in the apex of the thyroid gland. Other metastases were not discovered.

Sections from the colloid goiter showed atrophy and degeneration. The alveoli were decreased in number and lined with low cuboidal epithelium. Many were dilated and contained eosinophilic colloid. A few of them had colloid which took a basophilic stain. The stroma was greatly degenerated, the collagen being hyalinized and the nuclei absent.

The tumor in the apex of the thyroid gland consisted of a small-cell adenoma of the fetal type. The central portion contained mature alveoli, while peripherally the epithelium was arranged in columns, some of which had a lumen, while others did not show any attempt toward lumen formation. The epithelium was embryonal in type, with small nuclei rich in chromatin and scanty cytoplasm which stained deeply with eosin. There was colloid formation in a small number of vesicles. The stroma was delicate and contained few blood vessels.

Sections through the tumor from the rib showed columns of embryonal epithelium which were more differentiated than in the primary nodule in the thyroid in that the nuclei were vesicular and paler. They also showed a more pronounced tendency to form alveoli, and most of them contained eosinophilic colloid. Many of the alveoli were round; some were oval and elongated. The stroma was delicate but more abundant than in the original tumor, and it carried many more blood vessels with it.

## MUSCLE LESIONS ENCOUNTERED IN EXPERIMENTAL SCURVY. GILBERT DALLDORF.

This report is concerned with a striking lesion observed in the intercostal muscle of guinea-pigs. The animals were the subject of feeding experiments conducted by Dr. Walter Eddy at Teachers' College. Dr. Eddy was studying scurvy and had found that weight curves and gross appearances were often too indefinite to justify a diagnosis. In such cases, the animals were examined histologically.

The anatomic manifestations in experimental scurvy are well known and have been precisely described by many writers. When the established criteria for the

diagnosis of scurvy were employed, there was seldom difficulty in determining the presence or absence of the scorbutic process in the animals of this series, even when it was early or only partially developed. The changes at the junction of bone and cartilage in the ribs proved to be representative of the bone lesions of scurvy and technically simple to handle; hence, liberal samples were therefore taken from these areas.

Fifty guinea-pigs were used, ten of which were normal. The remaining forty were scorbutic, and the lesion to be demonstrated was found in twelve of these.

Scattered through the intercostal muscles were muscle fibers which had ruptured, often into several fragments. Such fragments were frequently surrounded by large endothelial giant cells. Layers of fibroblasts formed along the ruptured muscle cells, proliferating until they frequently formed a mass greater than the muscle itself. In addition, in some cases, large cells with acidophilic cytoplasm were found, frequently in process of mitotic division. These looked like muscle cells, and in some fields their activity was so great as to simulate a muscle cell sarcoma.

In other cases, the muscle cell proliferation was not present. The muscle remnants lay as hyalinized fragments in a matrix of lax connective tissue, poor in collagen.

The lesion varied greatly in extent. In some cases most of the intercostal muscles were involved; in others, only a few focal lesions were found.

It seemed impossible that the experienced and careful workers who had previously studied the disease might have missed such obvious lesions if they examined the muscles. It is true that most studies have been centered on the bony changes which have been considered the essential lesion. However, scarring in the muscles has frequently been described in chronic scurvy and has been considered secondary to changes in the bone.

The lesion described in this report occurred in early, acute scurvy, but the facts which suggest that it may be associated with the scorbutic process are:

1. The changes are found only in scorbutic guinea-pigs, although normal animals have been carefully searched.
2. The changes always appear in pigs in which the bone lesions are in an early stage of development.
3. They have many histologic features in common with the bone lesions with which they coincide.
4. They bear the same relationship to the muscle lesion found in chronic scurvy that the acute bone lesion bears to the bone lesion in chronic scurvy.

#### DISCUSSION

JAMES EWING: Dr. Dalldorf's slides were extremely interesting and surprising to me. I at first doubted whether they had anything to do with the scorbutic process, but the lesions occurred in such a high proportion of animals, and the control material was so adequate that I think we are justified in assuming that they are a part of the scorbutic process. The remarkable character of the lesion is interesting to the histologist; it suggests the extremely powerful influence of nutrition on the tissues. I think that the process in the muscle mainly concerns the muscle cells, and I could not convince myself that there was any participation of fibroblasts. I do not know of any parallel to such a process in the range of pathology.

HARRISON S. MARTLAND: It has occurred to me that in several metabolic diseases and a few of obscure infectious or toxic (?) origin there are circumscribed, possibly inflammatory, lesions in the subcutaneous tissues and muscles—the so-called fibrositis in chronic focal infections, nodes over the sacroiliac joints in gout, etc. Little serious study has been given these lesions from a histologic standpoint. In fact, we do not know very much about any of them. I am wondering if these muscle lesions in scurvy are not somewhat parallel, and have escaped notice clinically in human scurvy.

## Book Reviews

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TUMORS ARISING FROM THE BLOOD VESSELS OF THE BRAIN ANGIOMATOUS MALFORMATIONS AND HEMANGIOBLASTOMAS. By HARVEY CUSHING and PERCIVAL BAILEY. Price, \$7.50. Pp. 219, with 159 illustrations. Springfield, Ill., and Baltimore: Charles C. Thomas, 1928.

This is a monograph based on the systematic, clinical and anatomic studies of neurosurgical cases by the authors. There are two parts: one dealing with angiomatous malformations with fourteen illustrative cases and the other, the hemangioblastomas with ten cases. Each part has an exhaustive bibliography in which bracketed numbers indicate the pages in the text in which the work in question is discussed. The presentation is comprehensive, balanced, orderly and well illustrated. The publisher has done his part excellently. The summary gives the principal outcome so well that it is repeated here: "Blood vessel 'Tumors' of the brain may be divided into two major groups: (1) the angiomatous malformations and (2) the angioblastomas or true neoplasms of blood vessel elements. The angiomatous malformations are undoubtedly attributable to some fault of development, and they may be clearly distinguished from the blood vessel tumors proper by the fact that traces of compressed nervous tissue are invariably present between the vascular loops comprising the lesion. (1) The angiomatous malformations may be chiefly capillary (telangiectatic), chiefly venous (angioma venosum) or arteriovenous (angioma arteriale) in their composition. They more commonly occur in the cerebral hemispheres and are often provocative of epileptiform attacks, frequently Jacksonian in character. Only occasionally are these lesions found in the hind brain. Both the venous and the arteriovenous malformations are primarily surface lesions of the hemisphere, and three types may be recognized: a simple enlargement of a single vessel, a tangled enlargement of one or more vessels, or a more complicated (racemose) type in which the lesion extends from the cerebral surface like an inverted cone with its apex abutting on the ventricle into which a terminal hemorrhage not infrequently occurs. The venous angiomas, unless they are associated with trigeminal naevi, are not likely to be diagnosed until they are unexpectedly exposed at operation or autopsy. The arterial angiomas, on the other hand, may often be recognized by an audible bruit as well as by secondary effects of the aneurysmal (arteriovenous) communications which lead to enlargement of the extracranial vessels, of the carotids, or even of the heart. Whereas the venous angiomas are unaccompanied by a choked disc, the aneurysmal lesions are apt to be, and a unilateral exophthalmos is not infrequently produced. The treatment of any of these angiomatous malformations by surgical or other procedures, unless possibly by radiation, is unsatisfactory. (2) The angioblastomas are true tumors composed of angioblastic elements. They are rarely if ever accompanied by facial naevi, but that some of them at least, if not all, possibly have a congenitalanlage must be acknowledged in view of the fact that the lesions may be multiple. Their favored, if not their exclusive, site is in the cerebellum where they are often median tumors that appear to arise from a region near the posterior end of the fourth ventricle. They may be largely cystic or largely solid lesions. Histologically, they are conveniently divided into those predominantly capillary, those predominantly cellular, and those predominantly cavernous. It is rare, however, to find any tumor of pure type for they differ in degree rather than in kind. They have often been mistaken for vascular gliomas or meningiomas but they invariably show, when properly stained, a network of reticulum which serves to distinguish them from other growths. Some of the cerebellar hemangioblastomas are associated with a similar lesion in the retina (one case in our series of eleven), angiomas of the spinal cord, cystic kidneys, cysts of the pancreas, hypernephromos and other lesions. This represents a new disease which has familial tendencies



and should be known as Lindau's disease from its principal discoverer. The cerebellar hemangioblastomas like any other cerebellar tumors, should be treated, when possible by extirpation. Apart from the unusual vascularity of some of the lesions, they offer no unusual surgical difficulties. When cystic tumors are encountered, care should be taken to remove the mural nodule of the tumor for otherwise a recurrence of symptoms, due either to refilling of the cyst or to progressive enlargement of the tumor, may be expected."

AMERICAN TYPE CULTURE COLLECTION. CATALOGUE OF CULTURES. Ed. 2. (Distributed without charge.) Pp. 142. Chicago: The John McCormick Institute for Infectious Diseases, 1928.

Some evidence of the vitality of the American Type Culture Collection is given by this second edition of its catalogue, as a revision of its list of cultures has been made necessary by a considerable change in the content of the collection. During the past four years, the collection has grown from 750 to 2,000 cultures. Since the publication of the first catalogue, two years ago, 130 cultures have been discarded as impure, atypical or lost, and 650 cultures have been acquired. Of the 2,000 cultures listed in this edition, 1,100 are bacteria, 600 fungi and 300 yeasts. The private collections of Prof. F. W. Tanner, Prof. I. C. Hall and Dr. S. A. Waksman are still available through the generosity of the owners. In a similar manner, Dr. C. B. Sherbakoff, of the University of Tennessee Agricultural Experiment Station, has placed his large collection of *Fusaria* at the disposal of the curator.

The organisms are listed in alphabetical order under the names used in Bergey's Manual of Determinative Bacteriology as far as that system of nomenclature is applicable. The editors of the catalogue hope that the "liberal use of cross-references will facilitate the finding of organisms which are listed under unfamiliar names." Short of the publication of a complete synonymy, which would be unnecessarily expensive and laborious, these cross-references are certain to appear to be inadequate. An example of a puzzle to be worked out among these names is the problem before the medical bacteriologist who wishes to find the list of cultures of the "Friedländer bacillus." This familiar organism appears under the title of "Klebsiella," cross-reference: "*Bacterium mucosus capsulatus*." A closely related organism, listed in a cross-reference as "*Bacillus lactis aerogenes*" (not Bacterium) appears under the caption of "*Aerobacter aerogenes*." These seem to be inconsistencies and artificial separations. The nomenclature, however, is a workable one from the point of view of the cataloguer. This is not the place for any extended comments on bacteriologic nomenclature or for the expression of an inadequate opinion on uncertainties of the taxonomy of this branch of biology. It will be interesting, however, to observe what effect the use of the names chosen in this catalogue will have on the fixation and general use of the nomenclature set forth in Bergey's Manual.

Additional evidence of the service which this culture collection is rendering bacteriologists was given at the meeting of the Society of American Bacteriologists in Richmond in December, 1928, in a report from which Dr. L. A. Rogers has permitted the reviewer to make excerpts. During the past four years there has been a steady increase in the number of cultures supplied to bacteriologists. Since 1925, 12,913 cultures have been sent out in response to 2,553 orders for them. During the year 1928, 1,022 orders were received, and 4,761 cultures were sent out. Most of the cultures have been furnished for teaching purposes. Many, however, have been used for investigations. Of the total, 4,178 have been sent to institutions, 156 to individuals and 427 to commercial dealers in biologic supplies.

The staff of those engaged in the care of this collection has been increased by the appointment of Mr. W. R. Albus, as bacteriologist.

Although the Culture Collection has been of great immediate service to bacteriologists and, by the preservation of type strains, promises aid of inestimable value to investigators and other students in the future, it is faced by the problem of its own perpetuation. This is almost exclusively a financial problem. In 1929, the agreement of the General Education Board to contribute to the support of the

collection will have completed its fifth and final year. When the agreement was entered into, it was understood that an earnest effort would be made to put the collection on a self-sustaining basis. This effort has been made, but the collection is not self-supporting.

The administration has been economical, and no expense has been incurred for rent of quarters. Nevertheless, until 1928, income from the sale of cultures did not meet half of the expenses, and it is apparent that it will not be possible to maintain the collection in its present condition without assistance from other sources. It is also obvious that enlargement of the collection will be required to meet the increasing needs of bacteriologists. Those who have been in closest touch with the collection hope to see it increased, housed in an adequate building which would provide separate floors for bacterial and fungous cultures, and laboratories for special research, under the care of a larger staff of bacteriologists and mycologists. It would be a great misfortune if the collection were to be distributed on account of lack of financial support. Maintenance of the collection on a small scale would be less unfortunate, but would undesirably restrict its service. On the other hand, it would be greatly to the advantage of all interested in bacteriology if sufficient endowment could be secured to permit the collection to fulfil all its functions.

The curators of the collection again urge those who describe new species or make studies of older ones to send to the collection cultures, reports and references to their work. Contributions of this sort add new life and value to the collection.

GREEN'S MANUAL OF PATHOLOGY AND MORBID ANATOMY. Fourteenth edition. Revised and enlarged by A. PINEY, M.D., M.R.C.P. Pp. 650, with 261 figures and 7 colored plates. Philadelphia: Lea & Febiger, 1928.

Since the preparation of the thirteenth edition of the deservedly popular Green's Manual by Bosanquet and Wilson, Dr. Thomas Henry Green has died, but Dr. Piney, who has prepared the fourteenth edition, pays tribute to the continuing influence of the author. Dr. Piney has revised the sections on nephritis and surgical shock, and has made minor corrections and additions. There are numerous new illustrations, but none of the older ones has been replaced, which may be regarded as unfortunate because many are merely diagrammatic. The general character of the book remains unchanged. There are 416 pages of text devoted to general pathology and 219 to diseases of special tissues and organs. Of the part on general pathology, 86 pages are devoted to parasites, animal and vegetable, and 27 to immunity. The subject matter covered is extensive, but this description of the make-up of the book serves to indicate the brevity and conciseness of the presentation. It must also be remarked that extreme clarity prevails.

There comes a time in the life history of a scientific textbook or manual when simpler forms of revision are inadequate for the presentation of the progress recorded within its special field. A manual, such as Green's, is by its very nature principally for the use of students of medicine or related subjects. The introductory statement reads "The Art of Medicine must obviously be based upon a knowledge of the nature and the causation of disease, and it is this information that pathology attempts to supply." This objective, however, cannot be attained unless pathology is regarded as a living science, enlarging its observations, clarifying its hypotheses, broadening its experimental demonstrations and correlating its old and new facts. It is not nationalistic and cannot be covered by references almost solely to publications in the English language. Parasitology and immunology have become so extensive that their brief presentation in a book on pathology must of necessity be incomplete. Modern immunology draws on physical chemistry for its explanations and discards the Ehrlich diagrammatic and inaccurate hypotheses. The physiology of valvular defects of the heart is as deserving of discussion as that of nephritis. Subacute bacterial endocarditis is certainly of great clinical and pathologic significance. Rheumatic fever in relation to the heart and blood vessels should not be dismissed with two sentences. If endometrioma is

found in 30 per cent of gynecologic cases in which operation has been performed, it deserves consideration. Too great value is to be ascribed to the investigations of the Spanish school on the interstitial tissues of the central nervous system to have it neglected entirely. Metaplasia is not limited to epithelial cells. In spite of an "erratum" note concerning vitamin D in connection with rickets, the general discussion of vitamins should involve more than a consideration of vitamins A, B and C. There can be no satisfactory compromise between the older and newer views of nephritis. If shock is to be discussed, anaphylactic and allergic manifestations are too important in man to be omitted. These observations must make it apparent that a modest revision, singly or in series, cannot serve to modernize a book however excellent it was in its day and generation. Medicine is on wings, and he who would be with her and of her must fly to keep the pace. The author of a book which is to represent the scientific background of medicine must recognize these established advances.

**ORGANIC LABORATORY METHODS.** By the Late PROFESSOR LASSAR-COHN. An authorized translation from the general part of the fifth revised edition, by RALPH E. OESPER. Edited by ROGER ADAMS and HANS T. CLARKE. (No. 2 of the World Wide Chemical Series, edited by E. EMMET REID). Price, \$6.50. Pp. 469. Baltimore: Williams & Wilkins Company, 1928.

This translation of the general part of Professor Lassar-Cohn's well known book deals with the laboratory technic of organic chemistry. It contains a great deal of useful information concerning the basic principles of such fundamental procedures as distillation, crystallization, filtration and extraction. Its limitations for the worker in the biologic sciences are indicated in the translator's preface in which the aim of the book is described as being "to cite and outline the methods by which typical difficulties have been overcome and leave the adaptations of the suggestions to the problem at hand to the resourcefulness of the reader." The most serious defect of the book, from the standpoint of the biologist who wishes to apply the technic of organic chemistry to the specific needs of his own problems, is indicated by the fact that most of its many references are to papers written before 1900. There is thus no reference to such familiar methods as the use of collodion membranes in dialysis, or to the use of pyrex glassware, or electrical appliances of all kinds such as motors, drying ovens and hot plates. The book will appeal, therefore, to those interested in the broader aspects of the subject rather than to those interested in knowing whether methods exist which may be applied to the solution of the specific problem at hand.

**WILLIAM HARVEY.** By ARCHIBALD MALLOCH, Librarian, New York Academy of Medicine. Price, \$1.50. Pp. 103, with 10 full-page plates and 3 text illustrations. New York: Paul B. Hoeber, 1929.

This little book is the outgrowth of an address to commemorate the publication of Harvey's great book in 1628. It is a reprint, with corrections, from the *American Journal of Surgery*, September and October, 1928. Thoroughly familiar with the sources of information, Dr. Malloch sketches briefly the various phases of Harvey's life, with particular reference to the discovery that the blood moves in a circle. But no side of Harvey's activities or relations appears to have been neglected and the sketch, though brief, is unexpectedly comprehensive. Harvey's observations on the color of the lungs of the new-born and its significance are quoted. Pathologists may be interested in reading what Harvey, who was an experienced morbid anatomist, said on that point, namely, that lungs of fetuses having breathed "put on a white colour, and by this observation of the different complexion you may discover whether a mother brought her child alive or dead into the world; for instantly after inspiration the lungs change colour, which colour remains, though the foetus die immediately afterwards." Medical students, physicians and all who have any interest in the history of science and the lives of its leaders, will be grateful for Malloch's account of the life and work of Harvey.

## Books Received

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GREEN'S MANUAL OF PATHOLOGY AND MORBID ANATOMY. Revised and enlarged by A. Piney, M.D., M.R.C.P., Research Pathologist, Cancer Hospital, London. Fourteenth edition. Cloth. Price, \$7.50. Pp. 650, with 269 illustrations. Philadelphia: Lea & Febiger, 1928.

MICROBIOLOGY MONOGRAPHS, GENERAL, AGRICULTURAL, INDUSTRIAL. Edited by R. E. Buchanan, Iowa State College; E. B. Fred, University of Wisconsin, and S. A. Waksman, Rutgers University. Volume I. Morphologic Variation and the Rate of Growth of Bacteria. By Arthur T. Henrici, M.D., Professor of Bacteriology, the University of Minnesota. Price, \$3. Pp. 194. Springfield, Ill.: Charles C. Thomas, 1928.

RECENT ADVANCES IN BACTERIOLOGY AND THE STUDY OF THE INFECTIONS. By J. Henry Dible, M.D. (Glasgow), M.R.C.P., Professor of Pathology and Bacteriology in the Welsh National Medical School. Price, \$3.50. Pp. 363, with 22 illustrations. Philadelphia: P. Blakiston's Son & Company, 1929.

WILLIAM HARVEY. By Archibald Malloch, M.D. (McGill), M.R.C.P. (London), Librarian, New York Academy of Medicine. Price, \$1.50. Pp. 103, with 13 illustrations. New York: Paul B. Hoeber, 1929.

HISTORY OF MEDICINE. With Medical Chronology, Suggestions for Study and Bibliographic Data. By Fielding H. Garrison, M.D., Lieut.-Col., Medical Corps, U. S. Army, Surgeon-General's Office, Washington, D. C. Fourth edition, revised and enlarged. Cloth. Price, \$12. Pp. 996, with 286 illustrations. Philadelphia: W. B. Saunders Company, 1929.

HANDBOOK OF MICROSCOPICAL TECHNIQUE FOR WORKERS IN BOTH ANIMAL AND PLANT TISSUES. Edited by C. E. McClung, Ph.D., Professor of Zoology, University of Pennsylvania; Director of Zoological Laboratory, University of Pennsylvania. Price, \$8. Pp. 510, with 43 illustrations. New York: Paul B. Hoeber, 1929.

This book is designed for workers in all departments of biologic morphology. It meets the needs of the inexperienced worker who wants specific directions that he can use in handling general material. The major portion of the book describes the latest approved methods for the special technical purposes of experienced investigators. By means of cross references, needless repetition is avoided. The illustrations refer for the most part to instruments and technical procedures in microdissection, micro-injection and the staining of neuroglia and microglia. The book is a reliable and thoroughly competent guide in biologic microtechnology.

EXPERIMENTELLE STUDIEN ÜBER KNOCHENTRANSPLANTATION UND KNOCHEN-REGENERATION. Von Christian Rosing Bull. Pp. 105, with 17 illustrations. Oslo: Jacob Dybwad, 1928.

COLLOID CHEMISTRY, THEORETICAL AND APPLIED. By selected international contributors. Collected and edited by Jerome Alexander. Volume II. Biology and Medicine. Price, \$15.50. Pp. 992. New York: The Chemical Catalog Company, 1928.

VERHANDLUNGEN DER DEUTSCHEN PATHOLOGISCHEN GESELLSCHAFT IM AUFTRAGE DES VORSTANDES. Herausgegeben von dem derzeitigen Schriftführer G. Schmorl in Dresden. Pp. 564, with 148 illustrations. Jena: Gustav Fischer, 1928.



LEHRBUCH DER TOXIKOLOGIE FÜR STUDIUM UND PRAXIS. Von Ferdinand Flury, Professor der Pharmakologie an der Universität Würzburg, und Heinrich Zangger, Professor der gerichtl. Medizin an der Universität Zürich. Paper. Price, 29 marks. Pp. 500, with 9 illustrations. Berlin: Julius Springer, 1928.

PATHOLOGISCH-ANATOMISCHE VERÄNDERUNGEN ÜBER DIE CONGENITALE SYPHILIS BEI DEM FOETUS UND DEM NEUGEBORENEN KIND. Von Oluf Thomsen. Paper. Price, 20 crowns, Danish. Pp. 31, with 19 illustrations. Copenhagen: Levin & Munksgaard, 1928.

This is a reprint from a larger work by the author published in Danish in 1912. There are only sixteen pages of text, with nineteen plates in black and white illustrating the microscopic changes in congenital syphilis of the fetus and the newborn infant. The book gives a good presentation of the changes in congenital syphilis of the fetus and the newborn infant, but it does not add anything new to the knowledge of those changes.

THE KAHN TEST: A Practical Guide. By R. L. Kahn, Director of Laboratories, University of Michigan Hospital, Ann Arbor, Michigan. Price, \$4. Pp. 201. Baltimore: Williams & Wilkins Company, 1928.

MIKROSKOPISCHER NACHWEIS DER SPIROCHAETA PALLIDA, DER GONOKOKKEN UND DES ERREGERS DES ULCUS MOLLE. Von Dr. W. A. Collier, und Dr. A. Cohn, Berlin. Price, 5 marks. Pp. 92, with 4 illustrations. Berlin: Urban & Schwarzenberg, 1928.

AMERICAN TYPE CULTURE COLLECTION CATALOGUE OF CULTURES, 1928. Second Edition. Pp. 142. Chicago: American Type Culture Collection, The John McCormick Institute for Infectious Diseases, 1928.

VERHANDLUNGEN DES DEUTSCH-RUSSISCHEN SCHARLACH-KONGRESSSES VOM 11.-14. JUNI, 1928, IN KÖNIGSBERG PR. Herausgegeben von Dr. T. J. Bürgers, o.ö. Professor für Hygiene an der Universität Königsberg. Price, \$5. Pp. 400.

LECTURES ON CONDITIONED REFLEXES: Twenty-Five Years of Objective Study of the Higher Nervous Activity of Animals. By Ivan Petrovitch Pavlov, M.D., Director of the Physiological Laboratories, Institute of Experimental Medicine and Academy of Sciences; formerly Professor of Physiology, Military Medical Academy, Leningrad; Foreign Member Royal Society, Member of the Russian Academy of Sciences; Nobel Laureate, etc. Translated from the Russian by W. Horsley Gantt, M.D., B.Sc., Member of the American Relief Administration 1922 and 1923; co-worker in Professor Pavlov's Laboratory, Institute of Experimental Medicine, from 1925 to 1928. With the collaboration of G. Volborth, M.D., former assistant to Professor Pavlov at the Military Medical Academy; Professor of Physiology, University of Kharkov. An introduction by Walter B. Cannon, M.D., S.D., George Higginson Professor of Physiology, Harvard University. Price, \$6.50. Pp. 414. New York: International Publishers, 1928.